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THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS WITH PENICILLIN IN PEANUT OIL AND BEESWAX*

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THE apparent curability of subacute bacterial endocarditis with penicillin has been unequivocally established within the last two years.[1] The essentials of successful therapeusis consist of treatment with massive daily doses of penicillin for a month or longer, the actual amount given daily depending on the resistance of the infecting organism to penicillin and on the serum penicillin concentrations attained. Supplementation of the penicillin with heparin, as first advocated by Loewe and his associates,[2] has proved unnecessary in our experience[3] as well as that of others,[1] and the dispensability of this costly and usually troublesome adjuvant has gratifyingly simplified the therapeutic regimen. The necessity for prolonged and uninterrupted parenteral treatment in this disease, however, has imposed a considerable task on the professional attendants and has demanded no small measure of fortitude from the patients, who must either submit to intramuscular injections at hourly or two-hourly intervals night and day or tolerate continuous intravenous or intramuscular infusion for weeks and sometimes for months. These difficulties and objections could be largely eliminated if satisfactory and sustained serum penicillin levels were attainable, either with oral medication or by the infrequent injection of massive deposits of penicillin in a slowly absorbable form.

ORAL ADMINISTRATION OF PENICILLIN

The considerable destruction of penicillin in the stomach and the ready absorbability of certain drugs from the sublingual mucous membrane led to a preliminary trial of penicillin by this route in 3 patients. Penicillin was administered in small triturated tablets in 50,000-unit amounts, but no penicillin was detected in blood samples taken at half-hour intervals during the next five hours.

The ingestion of penicillin tablets, solutions or suspensions, with or without antacid buffering and adsorbing agents, is already well known to yield appreciable amounts of penicillin in the blood.[4] For the treatment of subacute bacterial endocarditis, however, this form of medication cannot yet be considered feasible — first because oral doses must be at least several times as large as parenteral doses to achieve comparable serum concentrations, which makes the cost of prolonged treatment prohibitively high, and second because it is necessary to repeat oral medication at about two-hour intervals night and day to maintain effective serum concentrations, and this is obviously objectionable when treatment must be carried on for weeks and months. For these reasons the treatment of subacute bacterial endocarditis with penicillin given orally has not been considered feasible thus far.

PARENTERAL DEPOSITS OF PENICILLIN IN SLOWLY ABSORBABLE FORM

Romansky[5] has recently developed a slowly absorbable preparation of penicillin for parenteral use by suspending the drug in a mixture of peanut oil and beeswax, and he has demonstrated that ample and prolonged concentrations of penicillin in the blood serum follow single injections of 1 cc. or more of a mixture containing 300,000 units per cubic centimeter.[6] Moreover, the therapeutic efficacy of this preparation in the cure of large numbers of cases of gonorrhea and syphilis given one injection daily has already been conclusively established.[7, 8]

During the past year we had a unique opportunity to compare the effect of penicillin in oil and beeswax with that of water-soluble penicillin in the treatment of a patient with subacute bacterial endocarditis who, although refractory to cure, could be kept asymptomatic, afebrile and with sterile blood cultures so long as he received at least 250,000 units of penicillin parenterally each day, either in two-hourly intramuscular injections or by continuous intravenous drip. If a similar therapeutic remission could be maintained indefinitely with a single daily injection of penicillin in oil and beeswax, continued hospitalization would no longer be necessary, and

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the patient might be able to survive without symptoms and with no more restriction or inconvenience than that imposed on a diabetic patient taking insulin. This result was achieved in the case that follows.

CASE 1. V. H., a 45-year-old engineer, in June, 1944, developed symptoms and signs of subacute bacterial endocarditis on a background of rheumatic heart disease with mitral and aortic valvular lesions. The infecting organism, *Streptococcus viridans*, proved inhibitable in vitro by penicillin concentrations of 0.04 units per cubic centimeter of culture. Treatment for 10 months with water-soluble penicillin in daily doses ranging from 240,000 to 600,000 units and administered either in fractionated intramuscular injections at two-hour intervals or by continuous intravenous drip was regularly attended by clinical remission and sterilization of the blood. Whenever treatment was interrupted to evaluate the clinical status, however, *Str. viridans* promptly reappeared in the blood. The extraction of an infected tooth and removal of the spleen, which were suspected as foci of reinfection, did not alter the course. The infecting organism did not change its resistance to penicillin in vitro during this long period. Although this 10-month treatment failed to cure the patient, it was apparent that he could be kept clinically well and with sterile blood so long as penicillin was regularly furnished.

Following a few test injections of penicillin in oil and beeswax in June, 1945, sustained treatment with this preparation* was begun in July and was continued until December 14. The injections, which were given intramuscularly, consisted of 300,000 to 450,000 units of penicillin, given either once daily or on alternate days in doses of 600,000 units. Treatment was periodically interrupted for brief intervals to evaluate the clinical status.

During the periods of daily treatment the patient remained afebrile and clinically asymptomatic, and the blood cultures were consistently sterile. The 600,000-unit doses at two-day intervals were abandoned after a month's trial because bacteremia was not consistently suppressed by this regimen. The patient gained several pounds in weight, gradually resumed an approximately normal level of activity and received permission to return to his work during the fall. That he was not cured, however, was apparent from the regular return of bacteremia within 2 weeks of any interruption in therapy. The patient kept a daily chart of his afternoon temperature for 6 months after his discharge, and throughout this period he remained afebrile. On one occasion, when treatment had been interrupted for 3 weeks, an Osler's node appeared on one finger, without other developments except bacteremia.

*The material was supplied for experimental use in this case through the courtesy of Dr. Charles Church, of E. R. Squibb & Sons, New York City.

The demonstration in this case that single daily injections of penicillin in oil and beeswax could maintain clinical remission and sterility of the blood just as effectively as had been previously accomplished with parenterally administered water-soluble penicillin encouraged us to try this form of therapy in the next case.

CASE 2. A. B., a 59-year-old housewife, had been ill for 5 months with fatigue, anorexia, periodic fever and night sweats. During this period she lost 35 pounds in weight. The past history included erythema nodosum in 1938, acute appendicitis in 1942 and typhoid fever at the age of 6, when, the patient asserted, a heart murmur was noted.

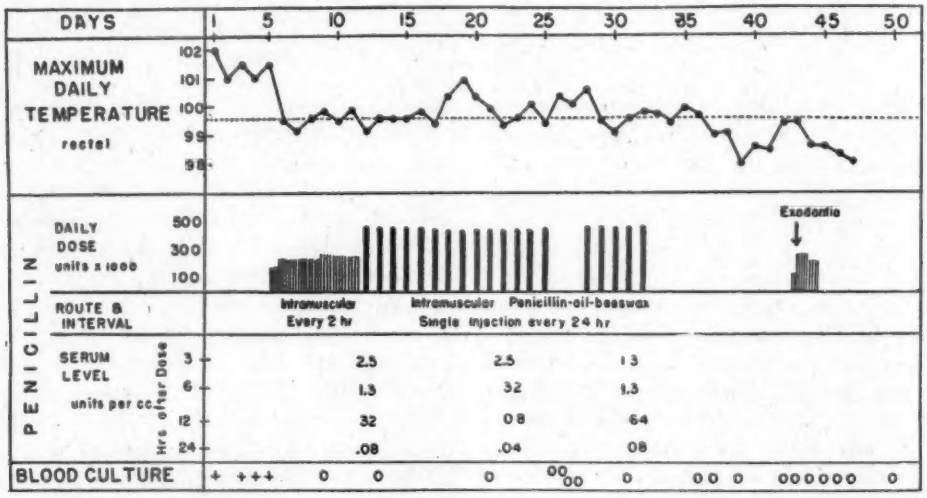

FIGURE 1. *Case 2.*

Physical examination disclosed an appearance of chronic illness but no wasting of the body. The heart, which was moderately enlarged, presented a harsh and moderately loud systolic murmur over the entire precordium, together with a faint systolic thrill at the apex. The liver edge was barely palpable, but the spleen was not felt. The finger ends were slightly club-shaped, and a fading petechia was noted over the left malleolus. There was a moderate hypochromic anemia with a white-cell count of 15,000 cells, 85 per cent of which were neutrophils. The blood was negative serologically, the urine was normal, and an electrocardiogram was normal. Roentgenograms of the chest showed moderate enlargement of the left auricle and ventricle. Four cultures of the blood revealed *Str. viridans* (two colonies per cubic centimeter) and the organism proved inhibitable by 0.02 units of penicillin per cubic centimeter of culture.

During the first 5 days, the rectal temperature reached 101 and 102°F., but within 24 hours of the commencement of penicillin therapy it fell below 100°F., and it remained there through most of the ensuing 6 weeks in the hospital. Following the preliminary administration of regular penicillin in doses of 20,000 units intramuscularly at 2-hour intervals for 6 days, treatment was changed to a single daily intramuscular deposit of 1.5 cc. (450,000 units) of penicillin in oil and beeswax, and the injections were continued for 19 days longer. Cultures of the blood continued sterile throughout the period of treatment, no petechiae appeared, and the appetite and strength soon returned. At about the midpoint of the penicillin course, slight clouding of vision on the right developed, accompanied by slight edema in the region of the macula, and continued for several days. Shortly before discharge an unerupted and a devitalized tooth were extracted, and penicil-

lin and sulfadiazine were given prophylactically for 2 days following the operation. The clinical course and laboratory data are illustrated in Figure 1. One week after discharge, generalized urticaria developed for several days.

Since termination of the formal course of treatment on November 16, 1945, the patient has continued entirely well and without congestive failure. She has gained 16 pounds in weight, and all of fifteen blood cultures have been sterile.

The apparently successful outcome in this patient treated almost entirely with penicillin in oil and beeswax led us to treat the next case with this preparation alone.

Case 3. M. W., a 40-year-old housewife, had had rheumatic fever at the age of 20 and was known to have had a heart murmur since then. In December, 1945, she developed insidious fever, drenching sweats and amenorrhea and lost 7 pounds in weight. Her physician noted several petechiae in the 2nd week of illness, and a blood culture made at that time yielded *Str. viridans*. Treatment with penicillin was begun promptly at another hospital, and the patient received 210,000 units daily for 25 days intramuscularly, in doses of 35,000 units every 4 or 5 hours. Although fever and symptoms subsided during the period of treatment, the patient relapsed both clinically and bacteriologically within a week of the termination of therapy. She entered the New Haven Hospital for further treatment on February 18, 1946.

The abnormal findings on admission included a temperature of 102.6°F., an Osler's node on a fingertip, two subungual hemorrhages and a petechia on an eyelid and another on the right breast. The spleen was barely palpable. The heart, which was moderately enlarged, presented a loud, harsh and long apical systolic murmur with wide transmission. The heart sounds were otherwise normal, and there was no congestive failure.

A moderate anemia without leukocytosis was present. Four successive blood cultures were positive for *Str. viridans* (10 colonies per cubic centimeter), and the organism proved inhibitable by 0.02 units of penicillin per cubic centimeter in vitro.

Treatment consisted entirely of intramuscular deposits of penicillin in oil and beeswax. Because a single injection of 1 cc. (300,000 units) was found to yield serum penicillin concentrations of 0.16 units per cubic centimeter at the end of 12 hours and less than 0.04 units at the end of 24 hours, it was decided to repeat the doses at 12-hour intervals, and this was done for 30 days. Symptoms subsided within a week, no further petechiae appeared, the spleen became impalpable, and the patient gained 4 pounds in weight. Cultures of the blood were sterile throughout the period of treatment and also during a deliberate interruption of therapy for 48 hours near the end of the therapeutic course. A moderate elevation of the erythrocytic sedimentation rate and an irregular fever of about 1°F., which persisted throughout the period of treatment, was attributed to the penicillin in oil and wax, for each deposit caused considerable local pain and some swelling, with occasional local redness. The temperature became normal within 48 hours of the cessation of the injections and remained so.

The treatment was stopped on March 25. The patient has remained asymptomatic and has resumed her household activities, and nine successive cultures of the blood have been sterile. She has gained another 4 pounds in weight, and the amenorrhea, which was present for 4 months, has given way to normal menstruation.

Serum Penicillin Concentrations

Intramuscular deposition of various amounts of the penicillin in oil and beeswax mixture in 5 patients yielded serum penicillin concentrations through forty-eight-hour periods, as shown in Table 1. Reasonably adequate levels were usually noted for twelve hours, and appreciable amounts of penicillin were often still present at the end of twenty-four hours. The fairly wide scattering of values at any time interval following an injection suggests either considerable variation in the relative rates of absorption and excretion of the penicillin or deficient potency of some of the doses. Most of the material had been supplied in 10-cc. vials, and it is conceivable that the reheating of such vials for successive daily injections of 1 cc. may have resulted in loss of potency. On the other hand, Romansky[6] claims from his much larger experience that this material is relatively heat-stable.

Table 1. *Serum Penicillin Concentrations.*

Dose	Hours following Injection						
units	1	3	6	9	12	24	48
	units/cc.	*units/cc.*	*units/cc.*	*units/cc.*	*units/cc.*	*units/cc.*	*units/cc.*
300,000	*0.64**	0.64	*0.64*	1.28†	0.32	0.08†	*0.04*
	0.08	*0.08*	*0.08*	*0.04*	0.16	0.04	*0.04*
					0.16	0.02	*0.04*
					0.08		0.04
					0.04		0.04
450,000		2.5	1.28		0.64	0.08	
		2.5	1.28	0.08	0.32	0.08	
		1.28	0.32		0.08	0.04	*0.08*
600,000				*0.64*		*0.08*	*0.04*
				0.64		0.08	0

*The italicized figures refer to Case 1.
†In a 3-year-old child.

Discussion

In the absence of previous reports of patients receiving penicillin in oil and beeswax for several weeks to months, observations regarding local and general untoward effects from such injections are of interest. The patient in Case 1 suffered only minimal local discomfort from the daily injections, practically all of which were given into the lateral aspects of the thighs. Slight local swelling was sometimes apparent for a few days, but even after six months of almost daily deposits there was no apparent local induration or lumpiness. It is also of interest that although this patient had a history of hay fever with occasional mild asthma, no allergic manifestations, either local or general, made their appearance in spite of several interruptions of the therapeutic course. The patients in Cases 2 and 3 suffered considerable local swelling and soreness, sometimes with erythema, which lasted for several days following each injection. The buttocks proved definitely preferable to other sites for the injections in these cases. In Case 2, a week following the last injection profuse urticaria developed for the first time in the patient's life. Five months later skin patch and scratch tests with penicillin, peanut oil and the penicillin-oil-wax mixture were performed, with negative results. Two slightly tender subcutaneous nodules, probably attributable to the previous therapy, were noted in the buttocks at that time.

In the beginning the handling and injection of the semisolid mixture proved extremely troublesome and difficult. Observance of the following technical details eliminated all difficulties. The ampule of material was kept at room temperature for a few

hours before use — it may be stored at room temperature — and was heated in water at 45°C. for several minutes to melt the material and render it injectable. The needles and syringe, which must be scrupulously dry, were also warmed to prevent cooling and congealing of the material during the injection. The warmed mixture, when flowing freely in the tilted vial, was quickly withdrawn through a 15-gauge needle into a 2-cc. or 3-cc. syringe with a snugly fitting piston; the air seal could be improved by applying a drop of sterile mineral oil to the distal half of the piston. The injection was made without delay through a 20-gauge needle. Lastly, more effective injection force was applied by the use of a syringe whose barrel was equipped with a pair of finger grippers.*

The attainability of considerable concentrations of penicillin in the serum for prolonged periods following single injections of penicillin in a mixture with oil and beeswax and the demonstration of the apparent curability of subacute bacterial endocarditis with this preparation given once or twice daily for several weeks offer a therapeutic regimen far simpler for both the patient and the professional attendants than any previously employed in the treatment of this disease. The question naturally arises whether, with this form of penicillin, patients may be treated at home and spared the long and costly hospitalization hitherto required. This would admittedly be feasible provided certain minimum bacteriologic controls were not neglected. The infecting organism in every case should be isolated from the blood, identified as a species reasonably inhibitable by penicillin and tested for its sensitivity to penicillin. Finally, one should have assurance that the concentrations of penicillin attained in the blood under the conditions of the treatment generously exceed the minimal inhibition level of the organism. To treat without such bacteriologic controls is to invite defeat through either inadequate dosage or too long intervals between injections — circumstances that may occasionally lead to increased resistance of the infecting organism to penicillin. Under circumstances in which bacteriologic facilities are minimal, some measures of control of the therapy may be achieved by the following simple and abbreviated procedure. One cubic centimeter of the patient's serum, previously warmed to 56°C. for five minutes to eliminate serum-inhibiting factors,[9] is diluted with three volumes of broth media and is inoculated with an eighteen-hour blood-broth culture of the patient's organism; a tube containing 4 cc. of broth only is similarly inoculated as a control for viability of the organism. Inhibition of growth in the tube containing serum implies that the penicillin concentrations are at least four times as high as the inhibition level of the organism concerned. Preliminary experiments for comparing this technic with actual measurements of the penicillin serum levels, with a minor modification of the method of Rammelkamp,[10] suggest that it is valid.

*Becton-Dickinson syringe (No. LC 3) was found highly satisfactory.

Two favorable factors probably contributed to the rapid apparent cure in 2 of our cases. In the first place, the infecting organisms proved relatively sensitive to penicillin in vitro. In the second place, satisfactory concentrations of penicillin were attained in the blood with either a single daily injection of 1.5 cc. or a twice-daily injection of 1 cc. The coincidence of such favorable circumstances cannot be taken for granted. Recent reports of extensive studies in patients treated for venereal diseases indicate that injections of 1 cc. (300,000 units) fail to maintain serum penicillin concentrations in excess of 0.10 unit for more than twelve hours in the majority of cases, and that more voluminous injections serve chiefly to raise the initial serum levels rather than to prolong the effects.[7, 8] One may infer from this that most cases of subacute bacterial endocarditis require injections at twelve-hour intervals to assure maintenance of serum penicillin levels high enough to inhibit the majority of strains of *Str. viridans*.

Summary

Apparent cure in 2 cases of subacute bacterial endocarditis due to *Streptococcus viridans* was effected with one or two daily injections of massive doses of penicillin in a mixture of peanut oil and beeswax.

In another case, which had proved refractory to cure after ten months' treatment with water-soluble penicillin given parenterally, an afebrile and asymptomatic state with sterility of the blood was maintained with a single daily injection of penicillin in oil and beeswax. Positive blood cultures, however, were obtained whenever this treatment was discontinued. It is believed that this patient can be kept indefinitely in a state of remission by this simple ambulatory form of treatment.

Satisfactory serum-penicillin concentrations were present for twelve hours and often for twenty-four hours following a single injection of 300,000 to 600,000 units of penicillin in oil and beeswax.

References

1. Keefer, C. S., and Anderson, D. G. Penicillin in the treatment of infections. In *Oxford Medicine*. Vol. 4. New York: Oxford University Press, 1945. P. 230.
2. Loewe, L., Rosenblatt, P., Greene, H. J., and Russell, M. Combined penicillin and heparin therapy of subacute bacterial report of 7 consecutive successfully treated patients. *J. A. M. A.* **124**: 144-149, 1944.
3. Goerner, J. R., Geiger, A. J., and Blake, F. G. Treatment of subacute bacterial endocarditis with penicillin: report of cases treated without anticoagulant agents. *Ann. Int. Med.* **23**:491-519, 1945.
4. Finland, M., Meads, M., and Ory, E. M. Oral penicillin. *J. A. M. A.* **129**:315-320, 1945.
5. Romansky, M. J., and Rittman, G. E. Method of prolonging action of penicillin. *Science* **100**:196-198, 1944.
6. *Idem.* Penicillin blood levels for twenty-four hours following single intramuscular injection of calcium penicillin in beeswax and peanut oil. *New Eng. J. Med.* **233**:577-582, 1945.
7. Romansky, M. J., Murphy, R. J., and Rittman, G. E. Single injection treatment of gonorrhea with penicillin in beeswax-peanut oil: results in 175 cases. *J. A. M. A.* **128**:404-407, 1945.
8. Kirby, W. M. M., Leifer, W., Martin, S. P., and Rammelkamp, C. H. Intramuscular and subcutaneous administration of penicillin in beeswax-peanut oil. *J. A. M. A.* **129**:940-944, 1945.
9. Elias, W. F., Merrion, H. J., and Speicher, T. Inhibiting factors in determination of penicillin in human sera. *Science* **102**:223-225, 1945.
10. Rammelkamp, C. H. Method for determining concentration of penicillin in body fluids and exudates. *Proc. Soc. Exper. Biol. & Med.* **51**:95-97, 1942.

STATISTICS OF DIABETES*

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THE statistics of diabetes will be considered under eight headings — prevalence of diabetes, characteristics of the diabetic population, mortality from diabetes, international comparisons, trend of diabetes in wartime, significance of geographical variations in diabetes, longevity of diabetic patients and use of statistics in clinical diabetes.

PREVALENCE OF DIABETES

The first consideration is the total volume of diabetes in the country. Frankly, it is not known with any degree of accuracy how many diabetic persons there are in the United States, but there is a certain body of facts on which to work. Some guidance can be gained from the annual death toll. In 1943, the last year for which statistics for the entire country are available, the number of deaths recorded as due to diabetes within the country was 36,314. At that time, there were approximately 2,500,000 Americans serving abroad in the armed forces, but the number of deaths from diabetes among them — the pick of the young men — was negligible. During the last five years, the number of deaths from diabetes has averaged nearly 35,000 per annum.

Not all deaths of diabetic persons are recorded as due to diabetes. There is a certain degree of understatement arising out of the fact that deaths of diabetic patients from such causes as cancer, tuberculosis and accidents are classified under these other causes. Thus, in 1940 in the United States, 3991 deaths were reported in which diabetes was secondary to some other cause, as compared with 35,015 in which it was the primary cause of death. The total number of persons reported as dying *with* diabetes, 39,006, was 11 per cent greater than the number recorded as dying from diabetes. In other cases, the diabetes has not been mentioned on the death certificate because the physician certifying the death did not consider that the diabetes caused it or because he did not know that the patient was diabetic. The study of Joslin and Lombard[1] indicates that the total number of deaths from diabetes may be understated by as much as 50 per cent. If one is conservative and assumes an understatement of 25 per cent, this means that the number of persons dying annually *with* diabetes is of the order of 45,000.

A rough approximation of the total number of diabetic persons may be made from the total number of deaths, together with such facts as are at hand on the longevity of these persons. The latest figures from the George F. Baker Clinic give the average duration of diabetes from onset to death as twelve years. Crude estimates based on life-table analyses of the mortality among patients of the clinic yield a somewhat higher figure — between fifteen and twenty years. These figures, however, are probably significantly higher than would be found true for the population as a whole. For example, a study in Philadelphia[2] showed a duration of only seven and five-tenths years. There are probably no more than 15 living diabetic persons per diabetic death. Applied to the reported number of deaths from diabetes, this would yield a figure of 525,000; applied to the estimate of persons dying *with* diabetes, it would yield one of 675,000.

The other sources of information on the number of diabetic persons are various surveys of the population. Three such sources will be discussed — the National Health Survey of 1935–1936 and the studies among selectees in Boston and in New Orleans.

The National Health Survey, conducted during the winter of 1935–1936 under the auspices of the United States Public Health Service, covered approximately 2,500,000 persons living in seven hundred thousand households in eighty-three cities. It was so planned as to constitute a representative sample of the general urban population of the country. Some rural families were canvassed but were excluded in the final analysis of data. The facts on disease as reported by members of households were recorded by trained enumerators. Wherever possible, an effort was made to confirm these statements through attending physicians. Among the families surveyed, 9182 cases of diabetes were reported, a total equivalent to 3.5 per 1000 population.[3] When the rates by sex and age were applied to the country as a whole as of the date of the survey, the resulting estimate of diabetic persons in the country was 450,000. Certain further adjustments of the figures, however, were made by the statisticians of the Public Health Service. The report of the National Health Survey contained an estimate of 660,000 diabetic persons in the country as of 1937.[4] Applying the prevalence rates by sex and age to the 1940 population yields a total of 500,000 diabetic persons in that year, and if the same adjustment were applied to this figure as was done in the 1937 estimate, the total in 1940 would be 725,000.

With regard to the National Health Survey, there are certain points to be emphasized. First, the survey estimate was based on the urban population covered. As will be seen, available statistics show

*From the Statistical Bureau, Metropolitan Life Insurance Company. A lecture given in the Postgraduate Course on Diabetes, Harvard Medical School, October 1, 1945.

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that, age being considered, the prevalence of diabetes is higher in the city than in the country. Hence, on these grounds, estimates for the country as a whole, based on the National Health Survey, would tend to be high. On the other hand, a survey such as this could not be expected to identify every case, a deficiency that is offset only in part by errors of the opposite kind — namely, the inclusion of persons reported as diabetic who were not so. It is not known which of the two factors — the use of urban data in the estimate or the unavoidable failure to include some cases in the survey — is of the greater importance. Apart from this, the method and extent of the adjustment of the basic figures of the survey that yielded the 1937 estimate of 660,000 are of doubtful validity. All in all, however, the basic unadjusted figures of the National Health Survey may be considered minimal.

Data based on Selective Service findings such as were reported by Blotner, Hyde and Kingsley[5] are significant in that such studies cover a relatively but not wholly unselected group of males within a certain age limit. Blotner and Hyde's figures for the Boston area are extraordinarily high — so high, in fact, that for reasons that have been published elsewhere,[6] one must be cautious about accepting them at face value. Thus, the prevalence rates in this sample, analyzed by age, were three to five times as high as in the National Health Survey. It is notable, moreover, that the number of previously known diabetic persons in the group was approximately what would be expected on the basis of the National Health Survey prevalence rates at these ages. These previously known cases constituted only one fifth of the diabetic total. Fortunately, efforts are under way to collect similar data elsewhere and to follow up the cases first diagnosed as diabetic on Selective Service examination, to see whether the diagnosis is confirmed on subsequent examination. Certainly, if the Blotner and Hyde figures are valid, this means a sharp upward revision in the estimates of the diabetic population, at least at the young adult ages.

In sharp contrast to the Boston figures are those published by Spellberg and Leff,[7] who reported on the findings at the New Orleans Induction Station during 1944. There, among 32,000 consecutive selectees, only 37 men with glycosuria were found, and of these only 9 were diagnosed as true diabetic patients. The proportion with glycosuria was thus only 1 per 1000, as compared with 8 in Boston. The corresponding figures for diabetes were 0.3 and 4.5 per 1000, respectively. Even eliminating the older men from the Boston series, because few of the New Orleans selectees in 1944 were over thirty-five, there is still a wide gap between the two studies. Spellberg and Leff cite a number of factors that bear on the situation, but the difference is too large to be accounted for by these factors alone.

Another important point regarding estimates of prevalence of diabetes is that the diabetic population is not static, so that any set of estimates needs to be revised periodically. The population continues to increase, and at the same time there is occurring a change in its internal composition that is significant with regard to diabetes — namely, the relative increase in the population at the older ages, and more especially the female population, among whom the prevalence of diabetes is highest. Other things being equal, this brings about a more rapid increase in the diabetic population than in the general population. Still another consideration is that the increasing longevity of diabetic patients will, for some time to come, at least, widen the margin between the number of new diabetic patients discovered each year and the number of such patients dying each year. An analysis based on the prevalence figures of the National Health Survey and the mortality among diabetic patients indicates that the number of new cases of the disease is at least 50,000 a year.[3] How much higher the actual figure is, one has no way of knowing, but it may be as high as 75,000 a year. This may be matched against the figure of 35,000 deaths from diabetes and the estimate of 45,000 deaths of persons *with* diabetes. On the basis of these figures, the annual increase in the diabetic population lies somewhere between 5000 and 30,000 a year. Computations based on the prevalence rates of the National Health Survey, together with estimates of future population, indicate a net increase of 10,000 diabetic patients a year.

Characteristics of the Diabetic Population

It is of interest to see how the diabetic population is constituted. The chief features of its makeup, in 1940, estimated from the prevalence rates of the National Health Survey, were as follows: 38.5 per cent of the diabetic persons were males and 61.5 per cent were females, a ratio of 10:16. In childhood and young adult life the extent and the prevalence rates of diabetes for males and females are approximately the same. Between the ages of thirty and eighty, there is a sharp sex divergence. The maximum difference in prevalence rates between the sexes is seen between forty-five and sixty-five, when the rates for females are approximately double those for males. There is some doubt whether there is any sex difference in diabetes prevalence rates in extreme old age because of the small number of observations at the later ages of life. Of course, there are many more aged diabetic women than men because at these ages women far outnumber men in the general population.

The prevalence rates in both sexes showed a steady increase with age to a maximum in the early seventies. At ages under thirty, less than 1 person per 1000 population was found to be diabetic in the

National Health Survey. In the early seventies, somewhat over 1.5 per cent of the male population and about 2.5 per cent of the female population, was found to be diabetic.

Mortality from Diabetes

The latest available national data on deaths from diabetes, those for 1943, showed it to be eighth in rank among the causes of death and seventh in rank among the diseases. Among white women over forty-five years of age, diabetes was fifth in rank among the causes of death. The importance of this disease in middle-aged and older women is shown by the fact that in 1943 it caused three times as many deaths among white women older than forty-five as did tuberculosis.

The country's death rate from diabetes in 1943, based on the 36,314 deaths recorded among persons resident in the country, was 27.1 per 100,000 estimated population. This was the highest crude death rate for diabetes recorded in the United States up to the present time. It must be borne in mind, however, that the rate was artificially somewhat increased by the absence abroad of large numbers of young men and women, among whom the death rate from diabetes is particularly low, since the armed forces exclude known diabetic patients. Indications are that the crude death rate fell moderately during 1944, as well as thus far in 1945. The present year's record is comparatively favorable because of the extremely low prevalence of respiratory disease during the past winter.

The trend of the recorded death rate of diabetes in the United States has been generally upward for the entire period during which statistics of causes of death have been assembled in this country. This has held true even since insulin became available for the treatment of diabetes. The highest rates in the country's history have been recorded in recent years. Facts for the country as a whole over the years are not available. Registration of deaths in many of the states was unsatisfactory until comparatively recent years, and only since 1933 have statistics for the entire country been available. In 1900, registration was satisfactory in only ten states and the District of Columbia. These comprise what are called the "Original Registration States." Studies in long-term trends of mortality are generally best related to the findings in these states, since they differ materially from the country as a whole in the composition of their population as regards sex, race and age.

In the Original Registration States in 1900, the death rate from diabetes was 11.0 per 100,000. In 1940, the rate in the same area was 35.5, or over three times the rate in 1900. In the later year, the rate for the entire country was 26.6 per 100,000. As has been indicated, an appreciable part of the rise in the diabetes mortality is due to the increasing proportion of older persons in the population. A recent publication of the Census Bureau[8] shows that when the sex-age specific rates for earlier years are adjusted to the 1940 population, the death rate for 1900 is increased from 11.0 to 13.0 per 1000, and the increase in the diabetes rate for the Expanding Registration Area is a trifle over 100 per cent after such adjustment, as against an increase of 140 per cent in the unadjusted rate.

The effect of the change in the age composition of the population on the death rate of diabetes is further shown by the fact that the average annual increase in recorded rates between 1921 and 1940 is 1.4 per cent when allowance is made for such changes, as compared with an increase of 2.5 per cent per annum before such allowance is made.

The increase in this death rate in the last decade or so has been comparatively slight. Between 1933, when mortality data first became available for the entire country, and 1940, the death rate, adjusted to the 1940 population distribution, increased only from 24.1 to 26.6, or a trifle over 10 per cent. Statistics of the Metropolitan Life Insurance Company show that between 1931–1933 and 1941–1943 the death rate of diabetes at all ages combined, when adjusted to allow for changes in the age and sex composition of the insured population, displayed a moderate decline among white males, a very slight increase among Negro males and a slight decrease among females, both white and Negro. Similar comparisons of 1941–1943 with 1921–1923 show a moderate decline among white males but substantial increases among white females and among Negroes of both sexes. When the data are analyzed by age, however, there are found substantial decreases at every age up to fifty-five among white persons of both sexes. It is thus only among older persons that increases in diabetes death rates are found, and such increases in recent years have been relatively small. Similar data by age for the United States between 1920 and 1940, undifferentiated as regards race and sex, show sharply lowered rates among young persons. The decline extends up to the age of forty-five, whereas marked increases in the rate are closely limited to the age of sixty-five and over.

Urban death rates from diabetes, regardless of the size of the city, are considerably higher than the rates in rural areas.[8] In 1940, the adjusted urban rate at all ages was over one and a half times as high as that in rural areas. In the aggregate, the rates for the cities show no marked differentials according to size of city. Such a differential does exist for females but not for males. In every group, however, the highest rate is found in the cities of 100,000 or more.

The mortality from diabetes among white persons is now little higher than that among Negroes. For both sexes combined, the white rate in 1940, adjusted for differences in the sex and age composition of the population groups, was 15 per cent above the Negro

rate. It is interesting to observe, however, that at most ages up to fifty-five, Negroes have appreciably higher death rates from diabetes than do Whites of the same age. After fifty-five, the situation is reversed. Among older people, the rates for Whites are double those for Negroes, or even more.

There is a distinct difference between the sexes with regard to the relative mortality from diabetes according to color. The rate for white females is only 3 per cent higher than that for Negresses, whereas the rate for white males exceeds that for Negroes by nearly 40 per cent. But as between city and country, females exhibit a notable difference according to color, the rates for Negresses in all classes of cities being higher than those for white females, whereas in the rural areas the rates for white females are appreciably higher than those for Negresses.

There are marked regional differences in the mortality recorded from diabetes. The rates are generally highest in the industrialized northeastern section of the country and lowest in the South and Southwest. Differences in the rates in part reflect differences in the age makeup of the population, and when these are allowed for the gap between the highest and the lowest states is appreciably narrowed.

A recent analysis of the crude or unadjusted rates shows that the increase in diabetes mortality is a country-wide phenomenon.[9] Comparison of the figures for 1940–1942 with those for 1930–1932 shows, curiously enough, that the increase has generally been most rapid in the states with the highest rates.

International Comparisons

There is comparatively little information on the trend of diabetes abroad since the war began. Consequently, any comparisons of this nature must chiefly rest on the situation before the war. At that time, the United States had the highest mortality from diabetes among the nations of the world. Generally speaking, the next highest death rates were recorded in certain countries of western Europe. The rate in Canada is appreciably less than that in this country, but a great part of the difference between the two countries is attributable to the younger average age of the Canadian population. In Europe the highest rates in prewar years were recorded in Denmark, Germany, Switzerland, Holland, England and Belgium. The rate in France was considerably lower, but French vital statistics are notoriously inaccurate with respect to causes of death. The recorded death rates in southern and eastern Europe were extremely low. This applies likewise to the few countries in Central and South America and to the few areas of the Orient for which figures are available. In contrast, the white populations in the English colonies and dominions show rates that are comparable to the figures in western Europe.

Prior to the war, an increase in diabetes death rates was practically a world-wide phenomenon in all the countries for which long-term records were available. It is notable, however, that after the use of insulin began, there was a sharp reduction in the rates among children and young adults in practically all the countries for which statistics are available. As in this country, the upward trend of the death rate at all ages combined reflected the increase in rates at the later ages of life.

Trend of Diabetes in Wartime

It was noted during World War I that there occurred an appreciable fall in the diabetes death rate in countries whose civilian populations were severely affected. There is comparatively little information on this matter for World War II. In the United States, Canada, Australia and New Zealand, the war had relatively little effect on the diabetes death rate. In England, on the other hand, the death rate from diabetes fell more than 20 per cent.

Significance of Geographical Variations in Diabetes

Many factors are responsible for the great range of variation in diabetes mortality, and presumably in morbidity also, from state to state in this country and from one country to another throughout the world. Particular mention has been made of such factors as the sex and age composition of populations. In general, it will be found that the reported mortality and prevalence of diabetes are greatest where the highest standards of living are found and where the general level of medical care and medical practice is farthest advanced.

The wide differences in the reported figures, after allowance has been made for obvious factors, are still further narrowed when a special effort is made to look for the disease. The survey of diabetes made in Arizona a few years ago by the state's physicians under the guidance and inspiration of Dr. Elliott P. Joslin showed this admirably.[10] Thus, whereas only two or three deaths are reported annually from diabetes among the Indians of Arizona, the survey, which covered at most only two thirds of the Indian population of the state, disclosed 73 living Indians with the disease. The estimated incidence of diabetes, based on the survey, was found to be of practically the same order as that recorded in the house-to-house canvass of 1929–1931 in Massachusetts and in the National Health Survey of 1935–1936. Moreover, the distribution of diabetes in Arizona was typical of that elsewhere: there were more diabetic women than diabetic men, and more old than young diabetic persons, the rate in the small population of Jews in the state was relatively high, and morbidity rates in special groups studied were comparable to those of similar groups elsewhere. It is likely, therefore, that where diabetes is least fre-

quently reported it is least accurately reported. Search for cases of the disease will be well rewarded.

Longevity of Diabetic Patients

As against the steady increase in the diabetes death rate in the general population, there is the striking paradox that diabetic patients, particularly since the introduction of insulin, have shown steady gains in longevity[11] and that this has been associated with improvement in their general health and working capacity.[12] The diabetic child of two generations ago could look forward to but a year or two of severely restricted life. Today, the expectation of life of the average diabetic child aged ten is estimated at forty years. Similar, though smaller, gains have been recorded among diabetic patients at other periods of life. Naturally, the gain is progressively smaller with increasing age. It is thus clear that the increase in mortality from diabetes in the general population can be explained only by a large and steady increase in the number of known diabetic patients. It is impossible in this lecture to go into the matter in detail, but the chief reasons are the increase in the proportion of older persons in the population, the more frequent discovery of diabetes as the result of improved diagnostic aids and the wider application of these measures, and certain environmental conditions that favor the onset of the disease in predisposed persons.

It is significant, furthermore, that life-table analysis of the causes of death among diabetic patients shows a reduction in the rates of death from most causes, especially those that reflect the degree of control of the diabetes.[13] Thus, the rate of death from coma has declined progressively and rapidly. This applies likewise in a measure to tuberculosis, pneumonia and even to gangrene. The new chemotherapeutic agents promise even further reductions in many of these causes and in particular, fortunately, in diabetic gangrene. Cancer is the only important cause of death to show some increase, and this is not unexpected in view of the similar trend in the general population and the increased longevity of diabetic patients.

The Use of Statistics in Clinical Diabetes

This discussion of the use of statistics in studies of diabetes is necessarily limited to certain broad considerations. Because of the rapid advances in the treatment of diabetes, and because it is a disease in which quantitative laboratory measurements are so important, there is more room and more need for statistics in clinical diabetes than in most fields of medicine. I need hardly remind this audience of the real differences of opinion that exist regarding the management of diabetes generally and of certain phases of the disease. The solution of the problems involved in these conflicting opinions can be expedited by the collection and analysis of clinical statistics by individual physicians or even by groups of physicians following more or less the same methods. The statistical method enables the physician to substitute facts for impressions on specific matters of treatment, as well as to compare results obtained with similar findings elsewhere. When such analysis reveals significant differences, it puts the physician on the alert to ferret out the causes and to introduce such changes in methods as the facts suggest. In teaching the subject of diabetes to medical students, the statistical approach is often effective.

There is also a broad field of community service to diabetic patients in which collection and analysis of statistics is of great importance and potential benefit. I refer to the study of the causes of diabetic fatalities in the community, in which a start has been made in several places, including Philadelphia and Cincinnati. As concerns the value of medical statistical studies of this nature, one should note the remarkable reductions in maternal mortality in many cities achieved as the result of a program of study of the causes of maternal deaths and the institution of a program to correct the faults disclosed. Progress against appendicitis also has been helped by statistical studies of community experience. In like manner, comparable programs in the field of diabetes conducted in cities or urban areas throughout the country should be effective in reducing the number of deaths from diabetic coma and even of those from diabetic gangrene. The statistics are, of course, not the cure for the situation, but they afford a solid basis of fact on which programs of public and professional educational efforts can be established.

A fundamental condition of reliable statistics on diabetes in clinical practice is a set of good records. There are required an adequate general record form on the history of the patient and subsidiary forms that give sufficiently detailed facts regarding his status from time to time and the methods of treatment used in diabetic emergencies. I urge you to look over the forms used at this and other leading clinics to see that your own records contain at least the essential items of information and that these records are complete and systematic. A greater degree of standardization in record forms than has yet been achieved is desirable. Further efforts along these lines should be encouraged.

One of the greatest needs in the field of diabetes, as well as in many fields of medicine, is long-range study of results of treatment. This means adequate follow-up of large numbers of patients. A fundamental consideration in such studies is that the follow-up be as complete and thorough as it is possible to make it. A 100 per cent result is desirable but, of course, not always practicable. Nevertheless, it should be the goal. In the follow-up studies of cases at the George F. Baker Clinic, all but 1 or 2 per cent of the patients have been located. The achievement of good follow-up results is largely a

matter of resourcefulness and ingenuity in locating difficult cases. Success in follow-up studies can be facilitated by preparing for them well in advance. It helps, for example, if the patient knows that such studies are contemplated or being made and that an effort will be made to check his progress periodically. It helps if, at the original visit or hospital stay, sufficient information is obtained — such details as the patient's business address in the case of employed persons, the school attended in the case of children and the given names of married women, together with the full name, age or date of birth and business and business address of the husband. In the case of patients who are referred by other physicians or who are seen in consultation, a cordial relation with these other physicians is invaluable, particularly if these men also know of one's interest in long-range studies of cases. Periodic communications with the patients or referring physicians are helpful. Finally, use may be made of outside agencies.

The importance of a high degree of completeness in follow-up studies cannot be overstressed. Failure to achieve this is a legitimate cause for questioning the validity of the results, because it is not safe to assume that untraced cases show the same general characteristics as do those that are traced; more particularly, if the number of untraced cases is disproportionate to the number of known deaths, the mortality figures are open to doubt.

Some groups are too large to make it practicable to follow up the entire number. In these circumstances, suitable sampling procedures are permissible. As an example, the last mortality tables computed for patients of the George F. Baker Clinic were based on a 25 per cent sample. Furthermore, the results of a systematically selected sample may differ widely from those based on an aggregate of unsystematic observations. An example of this is furnished by figures covering the average duration of disease and average age at death, as given in Tables 42 (page 275) and 44 (page 277) by Joslin et al.[11]

Certain necessary precautions must be given concerning the analysis of clinical statistics on diabetes. Characteristics and results may be expected to differ among diabetic patients according to age, sex, incidence of complications and environmental factors, such as education and social status. Allowance should be made for these various factors, if possible. In any case, the general nature of the group should be described. One must also be careful to define fundamental terms or the nature of specific classes studied in order to assess results with sufficient accuracy and fairness. The definition of diabetes is not fixed. Frank cases cause little difficulty, but borderline cases, if they form a significant proportion of the series, may be the cause of otherwise unexplained differences. Similar considerations apply with regard to the definition of diabetic coma and gangrene.

In long-range clinical studies of diabetes, profitable use can be made of the life-table method of analysis of mortality. The average duration of life from onset of diabetes to death is not an entirely satisfactory measure of the longevity of diabetic patients. This is seen most clearly with respect to diabetic children. Fatal cases among them are not typical of the group. Most diabetic children may be expected to outlive their physicians. It is therefore necessary in mortality studies of diabetic patients to consider the total population of such patients and the deaths that occur within it. From such data are computed death rates on an annual basis, in suitable categories by age and other characteristics. This method of analysis is described in a number of excellent texts and articles. Those deserving special mention are a book by Hill[14] and a paper by Frost.[15]

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It is too much to expect the physician to be a statistician with up-to-date knowledge of technical developments in this field. It is to the doctor's advantage, however, to have a knowledge of the fundamentals of statistics and statistical reasoning, and without too much trouble he can make himself familiar with a few basic statistical procedures. There are some textbooks on statistics that are especially designed for the physician, notably the volume by Hill already referred to. Those who are connected with or live near a large university would be well advised to make use of such professional statistical assistance as can be obtained there. In this way one is less likely to commit errors through faulty classification of data and to make unwarranted conclusions based on sparse data. The war has greatly stimulated work in practical and theoretical statistics. Consequently, statistical talent is now more abundant than ever before.

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References

1. Joslin, E. P., and Lombard, H. L. Diabetes epidemiology from death records. *New Eng. J. Med.* **214**:7-9, 1936.
2. Beardwood, J. T., Jr. Report of diabetes surveys in Philadelphia. *Am. J. Digest. Dis.* **11**:345-349, 1944.
3. Spiegelman, M., and Marks, H. H. Age and sex variations in prevalence and onset of diabetes mellitus. *Am. J. Pub. Health* **36**:26-33, 1946.
4. U. S. Public Health Service. Magnitude of chronic disease problem in United States. National Health Survey, 1935-1936. *Sickness and Medical Care Series*, Bulletin No. 6, 1938. 19 pp.
5. Blotner, H., Hyde, R. W., and Kingsley, L. V. Studies in diabetes mellitus and transient glycosuria in selectees and volunteers. *New Eng. J. Med.* **229**:885-892, 1943.
6. Marks, H. H. Discussion of Beardwood.[2]
7. Spellberg, M. A., and Leff, W. A. Incidence of diabetes mellitus and glycosuria in inductees with notes on some problems in diagnosis. *J. A. M. A.* **129**:246-250, 1945.
8. Department of Commerce, Bureau of the Census. Age-adjusted death rates in United States, 1900-1940. *Vital Statistics*, Spec. Rep. Vol. 23, No. 1, June 26, 1945. 40 pp.
9. Committee on Statistical Investigation, American Diabetes Association. Recent data on diabetes mortality. *Diabetes Abstr.* **4**: 4, 1945.
10. Joslin, E. P. Universality of diabetes: survey of diabetic morbidity in Arizona. *J. A. M. A.* **115**:2033-2038, 1940.
11. Joslin, E. P., Root, H. F., White, P., and Marble, A. *Treatment of Diabetes Mellitus.* Seventh edition. 783 pp. Philadelphia: Lea & Febiger, 1940. P. 279.
12. Metropolitan Life Insurance Company. *Diabetes in the 1940's: Clinical aspects based on the experience of the George F. Baker Clinic, Boston, and statistical studies by the Metropolitan Life Insurance Company, New York.* 20 pp. New York: Metropolitan Life Insurance Company, 1940. P. 13.
13. *Ibid.* P. 14.
14. Hill, A. B. *Principles of Medical Statistics.* Second edition. 189 pp. London: The Lancet, Ltd., 1939.
15. Frost, W. H. Risk of persons in familial contact with pulmonary tuberculosis. *Am. J. Pub. Health* **23**:426-432, 1933.

ANESTHESIA FOR RADICAL MASTECTOMY WITH INTRAVENOUS PENTOTHAL SODIUM AND INTERCOSTAL NERVE BLOCK*

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THE increasing use of Pentothal Sodium as an important anesthetic agent during major surgical procedures is well attested in the current literature on methods of anesthesia. That its optimal usefulness with the greatest measure of safety is achieved when it is employed in conjunction with supplemental anesthetic agents is borne out by reports relating to such conjoint use or by those that discuss in passing the supplemental use of other agents. My[1] previous report discussed the combined use of intravenous Pentothal Sodium and local nerve block (splanchnic) in upper abdominal surgery. In this earlier study, in which a new splanchnic needle guide was described, the two major purposes sought by the novocain nerve block were, first, to provide flaccid paralysis of the rectus abdominis muscle and second, to obliterate the visceral sensory impulses by splanchnic nerve block. By this rational supplementation of Pentothal Sodium with novocain block, a sharp reduction in the quantity of the former required for anesthesia was accomplished.

As surgical experience under Pentothal Sodium is extended, it becomes more and more apparent that one is dealing with an unusual opportunity to study accurately the precise physiologic background of surgical anesthesia in human beings. This premise turns on the evident dominance of the neurogenic reflexes initiated by surgical trauma during Pentothal Sodium anesthesia in reflexly activating the respiratory center; on the specificity of the respiratory response to the surgical reflexes arising from the segmental subdivisions of the terminal cerebrospinal nerves — cervical, thoracic, lumbar and sacral; and finally on the repressive action of Pentothal Sodium on the reflexly activated center.

The first site of pharmacologic action by Pentothal Sodium is the cerebral cortex, whereby unconsciousness supervenes; the second site appears to be the thalamus, whereby all reflex motor response to surgical trauma is controlled as a result of suppression in this relay center of all sensory impulses directed toward the cortex; the third site of action is the respiratory center, whereby, in the absence of reflex stimulation from surgical trauma, there is a completely smooth graded depression of respiratory activity. Under the conditions of a surgical operation, however, painful (noxious) stimuli of constantly varying intensity are conducted from the field of operation over the afferent limb of intact reflex arcs to the respiratory center. Depending on whether the inspiratory or expiratory neurons are specifically activated, the afferent limbs of the arcs carry back impulses that alter the character of respiration in a specific manner. Thus, the effective administration of Pentothal Sodium as an anesthetic agent resolves itself into an effort to achieve an optimal yet safe balance between the depressing action of this drug on the reflexly activated respiratory center and the stimulating action of neurogenic stimuli impinging on it that have been initiated by trauma in the field of operation. The goal sought in effectuating this balance is that of respiratory quietude without undue depression of respiration.

The introduction of novocain nerve block in anesthesia under Pentothal Sodium is directed at strategically placing the solution so as to interrupt transfer of noxious afferent stimuli centrally, thus minimizing the reflex stimulation of the respiratory center. By such a physiologic maneuver the intermittent demands for increased administration of Pentothal Sodium are eliminated and the total overall demand for the drug is sharply reduced. My experience during the last two years with the systematic combined use of these two methods of anesthesia has sustained experimentally in human beings the following generalization made in 1945 by Gordh.[2] "The more the physiology of anesthesia is studied, the more strikingly becomes the predominance of the part played by respiration. Indeed the physiology of respiration may be said to dominate the physiology of anesthesia."

The present study continues the report of my experiences with the combined use of Pentothal Sodium and local nerve block as a method of anesthesia in major surgical procedures. The present report specifically discusses the use of intravenous Pentothal Sodium combined with intercostal nerve block in the performance of radical mastectomy for carcinoma of the breast. It is based on a comparative study of two groups of cases. The first group consists of four radical mastectomies performed under Pentothal Sodium alone. The second group consists of six radical mastectomies performed under Pentothal Sodium and supplemental intercostal novocain block. An interesting result of the combined method is that the surgeon becomes an active participant in the production of the anesthesia, since all novocain blocking is carried out by the surgeon via a transincisional approach after the incision has been made. By this method the surgeon may

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place the novocain solution strategically, precisely and visually. Many surgeons, having been trained in the technic of novocain field block, have discarded it as a time-consuming, delaying method under conditions in which the surgeon must administer it himself in the course of a heavy surgical schedule. The use of this technic by the transincisional approach and in conjunction with Pentothal Sodium, however, restores novocain field block to the status of a precise, quickly executed technic, which proves of great value in the restricted physiologic roles herein demanded of it.

The method of combined intravenous Pentothal Sodium and intercostal nerve block in radical mastectomy is essentially simple. The patient is carried into a light third stage of surgical anesthesia with Pentothal Sodium, which permits a skin incision to be made. In this study the drug was administered in a 1 per cent solution according to the fractional drip method previously discussed. Using the Greenough modification of the Rodman incision, the posterior axillary incision is made and carried down to the ribs and intercostal muscles for the entire length of the operative field. The skin and subcutaneous tissues are dissected posteriorly beyond the point of emergence of the lateral cutaneous branches of the intercostal nerves. With the fingers of the left hand identifying each rib successively from the eighth or ninth upward to the fourth, a needle is advanced under the lower border of each rib until it penetrates the compartment between the external and internal intercostal muscles in which each intercostal nerve runs, and here 2 or 3 cc. of a 1 per cent solution of novocain is deposited. The axilla is then dissected sufficiently to expose the upper four ribs and to identify and protect the axillary vessels and nerves, following which the four upper intercostal nerves are similarly novocainized. The deposition of novocain should be made posteriorly to the midaxillary line, which is the point of emergence of the lateral cutaneous branches of the intercostal nerves. By this transincisional method, a quick, accurate blocking of the intercostal nerves under vision may be easily accomplished in two or three minutes. The mastectomy may then be completed with need of but little more Pentothal Sodium.

In the first group of 4 patients, to whom Pentothal Sodium alone was administered without the use of nerve block, the drug had to be administered at the average over-all rate of 23 mg. a minute for the duration of the entire procedure (induction, operation and closure). In the second group of 6 cases, in which Pentothal Sodium was supplemented by transincisional intercostal nerve block performed by me, the administration of the drug was sharply reduced to an average over-all rate of only 13 mg. a minute, a reduction of nearly 50 per cent. In 1 case following establishment of the intercostal block, no further administration of Pentothal Sodium was required. In all cases in which intercostal nerve block was established, minimal additional amounts of the drug were needed following the initial induction dose. As an example, a patient required 1 gm. (100 cc. of 1 per cent solution) of Pentothal Sodium for induction, whereas after establishment of the intercostal block only 200 mg. (20 cc.) was needed over a period of one hour for the entire mastectomy. Although the number of cases in each group is small, nevertheless the dramatic reduction in this rate of utilization of Pentothal Sodium validates the conclusions drawn as to the importance of the supplemental use of local nerve block in the operative field. The significance of the intercostal block from the viewpoint of the physiology of surgical anesthesia is that the noxious impulses from the operative field were blocked; they were not conducted centrally and neither impinged on nor stimulated the respiratory center. As a consequence, patients were carried in a light plane of anesthesia with quiet, unstimulated respiration during the entire procedure.

Discussion

The conclusion derived from these successive studies is that the fundamental base from which a consideration of the physiology of surgical anesthesia may properly proceed is the dominance of specific surgical reflexes in so far as they stimulate the respiratory center and activate the respiratory mechanism. This concept accurately integrates with the increasing recognition in recent years of the importance of neurogenic stimulation of the respiratory center, as contrasted with its chemical stimulation. The painful (noxious) stimuli of surgical trauma, whether from the somatic or visceral zones, are conducted centrally and impinge on the respiratory center, stimulating it to activity, preponderantly on the inspiratory or on the expiratory side. The type of response depends on the peripheral segmental representation of the cerebrospinal nerves in the field of trauma — whether cervical, thoracic, lumbar or sacral. The anatomic specificity of reflexes from the different segmental areas of operation has been recorded and demonstrated by me with pneumographic recordings.

The segmental character of the respiratory response to neurogenic stimuli initiated by surgical trauma may be briefly outlined as follows.

Cervical segment. Little stimulation of the respiratory center is evident from surgical trauma in this area, as evidenced by observations made during thyroidectomies. Few opportunities were available for studying respiratory response during operations on the upper extremities. In 1 case, traction on an exposed median nerve sharply stimulated the center.

Thoracic segment. The wide area of the body supplied segmentally by the intercostal nerves extends from the neck to the symphysis pubis. In all operative procedures in this segmental zone, in the somatic plane, the same characteris-

tic respiratory response is elicited and may be strikingly recorded by a pneumograph. There is a transient stimulation of the inspiratory phase of respiration. There is a sharp and prolonged stimulation of the expiratory phase, characterized by a succession of respiratory cycles in which the phase is intensified and prolonged for four to twelve seconds. In a few cases traction on the upper abdominal viscera has produced a nearly complete expiratory arrest. This prolongation of expiration is due to the fact that the expiratory phase has been converted from a passive to an active phenomenon. The accessory muscles of respiration, particularly the rectus abdominis, internal and external oblique and transversalis muscles, are reflexly and fully activated during expiration, so that they retract the lower ribs downward and inward during the expiratory phase for varying periods of time. In light planes of anesthesia this effort may be accompanied by an expiratory grunt. Increased quantities of Pentothal Sodium depress the more sensitive and reflexly stimulated expiratory neurons, doing so far in excess of the drug's depressing action on the inspiratory neurons. By this action the distorted inspiratory-expiratory ratio, which may be 1:5 or 1:6, is normalized and restored to the usual 1:1 ratio. At this point the accessory muscles are no longer activated, the expiratory phase returns to a passive state, and respiratory quietude again prevails. The reflexes from the thoracic segment when initiated in the skin and subcutaneous tissues may be blocked by novocain infiltration or by inhalation of nitrous oxide and oxygen. In the field of radical mastectomy they may be interrupted by an intercostal nerve block; when arising from the subdiaphragmatic visceral zone they may be interrupted by splanchnic block; and when arising from manipulation of the bowel they may be interrupted by mesenteric block. The peritoneal traction reflex, initiated during closure of the incision and transmitted centrally by the somatic intercostal nerves, may be easily suppressed by small quantities of cyclopropane or of nitrous oxide and ether. The more profound visceral and peritoneal traction reflexes are not controlled by inhalation of nitrous oxide and oxygen alone with Pentothal Sodium.

Lumbar segment. The reflex stimulation of respiration from the zone of lumbar-nerve distribution is mild as compared with that from the thoracic zone. There is a mild increase in the rate and amplitude of both inspiration and expiration; the normal ratio of the two phases is preserved; expiration does not become an active phase, so that the accessory abdominal muscles of respiration are not activated; and abdominal quietude is consequently not disturbed. The lumbar reflex may be demonstrated by traction on the superior hypogastric plexus during a presacral neurectomy. This reflex may be obliterated by novocain block above the level of traction. In clinical surgery this reflex is not often encountered. It is generally seen in the presence of extensive pelvic inflammatory disease or endometriosis, when the adnexa have to be forcibly separated from the pelvic parietal peritoneum. In the somatic area the reflex may be noted during operations on the lower extremities in the zones of lumbar-nerve distribution. This reflex is quite easily controlled by small additional quantities of Pentothal Sodium.

Sacral segment. The sacral reflex is strikingly characteristic and different from the reflexes elicited in the other segmental zones. It arises only from the deep pelvic zones in cervicovaginal regions in the female and in the prostatic regions in the male. During pelvic surgery strong traction on the cervical region may evoke a single prolonged inspiratory effort, accompanied by a loud inspiratory moan due to reflex laryngospasm. No succession of repeated respiratory responses is established as is characteristic of the thoracic and lumbar reflexes. The sacral reflex may be blocked by novocain placed deeply in the curve of the sacrum or by infiltration of the uterosacral ligaments at their point of attachment to the cervix. These ligaments have in this manner been experimentally revealed as the pathway for transfer of the sensory nerves responsible for this distinctive sacral reflex. This reflex may also be elicited from trauma to the penis during a circumcision, by impulses transmitted over the dorsal nerve of the penis to the internal pudendal nerve and thence to the sacral plexus. In the somatic areas the reflex may be elicited over the saddle area of distribution of the sacral nerves in the region of the anus, inner thigh, vulva and scrotum. The sacral reflex has no significance in so far as quietude of the operative field is concerned. Its constant repetition may, by virtue of its noisy laryngospasm, be a source of annoyance to the surgeon and the anesthetist.

Summary

Further experiences with the use of combined intravenous Pentothal Sodium and local nerve block anesthesia are presented. A previous report described the sharp reduction in the rate of utilization of Pentothal Sodium for upper abdominal surgery following the supplemental use of splanchnic nerve block. In the present study a comparable sharp reduction in the rate of utilization of the drug during radical mastectomy for cancer of the breast following the supplemental use of intercostal nerve block is reported. This observation is related to the physiology of surgical anesthesia in so far as the quantity of Pentothal Sodium required for a satisfactory anesthesia is directly proportionate to the amount needed to repress the activated respiratory

center, which has been reflexly stimulated to overactivity by noxious stimuli arising from the operative field. By the strategic use of novocain block by a simplified transincisional approach, these stimulating impulses are prevented from reaching and activating the respiratory center. Thus, the excessive demand for Pentothal Sodium to control the reflexly stimulated center sufficiently to restore respiratory quietude is circumvented.

A brief résumé of the specific segmental character of the surgical reflexes and respiratory response evoked from the different body areas has been given, in so far as they evoke a characteristic response from the respiratory center. These have been recorded by pneumographic tracings.

A general statement with reference to the combined use of the two methods of anesthesia may be made. On the basis of a physiologic integration of methods, the Pentothal Sodium induces quiet sleep that is free from any excitement; it provides a quiet respiration by repressing the stimulation of the respiratory center from the less intense surgical reflexes; it provides a comfortable recovery period singularly free from nausea and vomiting and from pulmonary complications. Strategic transincisional novocain block provides relaxation of muscles; it may be used to block massive reflex impulses from stimulating the respiratory center, — intercostal, splanchnic, mesenteric or pelvic block, — thus reducing the demands for large quantities of Pentothal Sodium. The terminal use of small quantities of cyclopropane or of nitrous oxide and ether to control the peritoneal traction reflex at the time of closure of the incision eliminates the final large peak demand for Pentothal Sodium, thus contributing to the early awakening of the patient.

This rational integration of methods in terms of the basic physiology of surgical reflexes and respiration during anesthesia and surgery has provided an eminently safe and satisfactory method of anesthesia for over 70 per cent of general surgical operations.

References

1. McCann, J. C. Anesthesia by combined intravenous Pentothal Sodium and local nerve block. *New Eng. J. Med.* 233:55-58, 1945.
2. Gordh, T. Postural circulatory and respiratory changes during ether and intravenous anesthesia: experimental analysis of significance of postural changes during anesthesia with special regard to value of head-down posture in resuscitation. *Acta chir. Scandinav.* (Supp. 102) 92:1-126, 1945.

MEDICAL PROGRESS

ACTIVE IMMUNIZATION (Continued)

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BOSTON

Pertussis

Despite the fact that infant deaths from pertussis have decreased 70 per cent in the last forty years, it remains the most frequent cause of death among the acute contagious diseases of early childhood: "The concentration of deaths in the first two years of life, especially under six months, is constant for all parts of the United States."[193] A recent editorial[194] points out that in Massachusetts from 1924 to 1943, 58 per cent of all deaths from this disease occurred in the first year of life, and 84 per cent in the first two years. Furthermore, the disease in older children, although rarely fatal, is frequently prolonged and debilitating, and involves much time lost in isolation and away from school. Hence there is ample justification for the numerous attempts that have been made to control the disease by means of immunization.

During the last fifteen years, beginning with the work of Leslie and Gardner[195] on the antigenic phases of *Haemophilus pertussis*, the principles underlying artificial immunization against whooping cough have been sufficiently elucidated to make possible the production and use of vaccines that, in most of the studies reported, protected a large majority of the persons immunized. The development of pertussis vaccination up through 1942 has been reviewed by both Lapin[196] and Felton and Willard.[197] With few exceptions, the studies reviewed have demonstrated in large groups of children that the communicability rate of pertussis in persons vaccinated with 70 to 120 billion killed, whole, virulent pertussis bacilli is much less than the expected rate as determined by experience in unvaccinated children. Similar results are found in the more recent reports of Bustamante,[198] Galvin and Wampler[199] and Garvin.[200] Moreover, attempts to evaluate the severity of the pertussis occurring in both groups, generally revealed that fewer severe cases occurred in the vaccinated than in the control groups. These findings have in general indicated that vaccination resulted in from 75 to 90 per cent protection. Such field studies have been criticized, on the basis that the unvaccinated groups used for comparison were not valid controls.[201] This criticism has in some cases been justified, and it is fair

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to demand that the study and control groups be submitted to an independent test of random selection, such as a comparison of the incidence of other communicable diseases in both groups.[202,203] An interesting method of analysis is that of Sargent and Merrell, which has been applied to pertussis immunization by Weiss and Kendrick.[204] They compared the incidence of pertussis among immunized and nonimmunized children under ten years of age reported during a given period as having contracted scarlet fever, measles, chicken pox or pertussis. From these data and from the pertussis immunization files, it was possible to compare the expected incidence of pertussis, if the immunization had been of no value, with the actual incidence. Only 15.8 per cent of the expected cases occurred in the immunized group. In passing it should be noted that the 34.8 per cent attack rate, sometimes cited[205] from Kendrick and Eldering's major study[203] as being in essence a failure, occurred among children experiencing intimate exposure to the disease — the control group showing a communicability rate of 89.4 per cent. To be fairly evaluated, such figures should be compared with similar studies of the effectiveness of a generally accepted bacterial vaccine in the presence of an equally high attack rate among the controls. Such a comparison would be difficult, for few bacterial infections occur under conditions leading to a 90 per cent attack rate.

Except for the widely discussed study of Doull et al.[206] in Cleveland ten years ago and the subsequent unfavorable one of Siegel and Goldberger,[207] most reports indicate that a significant degree of protection is obtained with pertussis vaccine. The failure of the Cleveland immunization program has been generally attributed to the fact that the vaccine was washed in distilled water, a procedure since suspected of being injurious to the antigen and not employed in any other major study until the recent British trial of pertussis vaccine reported by McFarlan et al.[208] who apparently used an ample vaccine dosage as judged by bacterial counts and whose study was well controlled. Among 350 vaccines the incidence of pertussis scarcely differed from that in the control group. On the basis of these findings and those of Doull et al. and Siegel and Goldberger, a concurrent editorial[201] concluded that the favorable reports of the last ten years are open to question. The editorial ignored or minimized the facts that the British vaccine was grown on horse-blood medium, which has been shown to favor rapid loss of antigenicity in *H. pertussis*,[209] that the studies of McFarlan and Doull and their associates — the only two in which the vaccine was washed in distilled water — represent two of the three important failures of pertussis vaccination in the last decade, and that the British vaccine was held in phenolized distilled water at icebox temperature for a week, which would presumably have accentuated whatever injury may be done by distilled water. The burden of proof appears to lie with those who do not consider washing in distilled water to be harmful; in any event, a comparable study is now being carried out in England, using a generally accepted vaccine of American make.

Undoubtedly there is considerable room for improvement in pertussis vaccines and vaccination. The protection rate, although it may be highly satisfactory from an epidemiologic point of view, is not entirely so to the practicing pediatrician. The chances of protection cannot well be enhanced by an increase in the dosage of the standard vaccine, which is already high in volume (up to 7 cc. in some schedules), in numbers of bacteria (70 to 120 billion) and in numbers of doses (three to five); also, the procedure is followed by a relatively high incidence of local and general reactions. On the other hand, the dosage cannot wisely be reduced. There are, however, various ways of increasing the effectiveness per unit dose of the vaccine. Lapin et al.,[210] Miller and Saito,[211, 212] Coppolino[213] and Mishulow et al.[214] favor intervals of two to four weeks between doses. Although no comparative clinical studies have proved that a longer interval yields superior protection, such a supposition is reasonable in the light of numerous studies on other immunizing procedures cited elsewhere in this review.

Alum-precipitated pertussis vaccine was introduced several years ago by Harrison, Franklin and Bell,[215] who found a single dose of 10 billion organisms prepared in this fashion to be insufficient; Bell[202] subsequently showed, however, that two such doses at an interval of four weeks gave a high level of protection, and similar results were obtained by Kendrick.[216] The use of aluminum hydroxide absorption has recently been reported,[217] and may represent a possible improvement over alum precipitation, since the reactions appear to be somewhat milder.

Until recently, all successful pertussis vaccines were prepared on some modification of the classic Bordet-Gengou type of blood-starch-agar medium, either human (Sauer) or sheep (Kendrick) blood being used. Hornibrook[218] had shown that *H. pertussis* could be sustained in Phase I for several generations in a liquid medium of relatively simple composition. Wilson,[219] Taylor and Farrell[220] and Cohen and Wheeler[221] introduced successive improvements, so that rapid adequate growth of a virulent, antigenic form of the organism can be obtained in this type of medium without the necessity of introducing red blood cells or foreign protein in any other form. Such a medium approaches the ideal for its purpose, since it minimizes the chances of inducing untoward reactions to substances of high molecular weight while retaining a maximum of the antigenic material present in the original growth.

The numerous attempts to evaluate the significance of the toxins of *H. pertussis* have been well reviewed by Lapin.[196] Several recent studies lend sup-

port to the long established belief that a toxic factor contributes to the pathogenesis of pertussis. Sprunt and Martin[222] showed that the edema, necrosis and mononuclear reaction that can be induced in rabbit lungs by pertussis toxin could be prevented by an antitoxin produced in rabbits. Ospeck and Roberts[223] found that the same antitoxin furnished more effective protection against live *H. pertussis* cultures than an antibacterial serum. Evans,[224] in a carefully controlled study, presented evidence that parenterally administered pertussis antitoxin offered little protection against pertussis bacilli introduced intranasally, whereas intranasally applied antitoxin exerted a more marked protective action than an antibacterial serum. Such findings suggest that antitoxic titers in human beings should bear some relation to resistance to pertussis, but a study in patients convalescing from pertussis showed that detectable titers were rarely found.[225] Moreover, an intradermal susceptibility test based on Strean's[226] endotoxin failed to reveal a definite correlation either with a history of pertussis or with previous vaccination.[227] Finally, the detoxified pertussis antigen developed by Roberts and his associates, when submitted to a recently reported field trial, did not appear to afford significant protection.[228] One must conclude, therefore, that the role of the toxic factor in susceptibility or resistance to pertussis infection has yet to be elucidated.

The combination of pertussis vaccine with other antigens was first suggested ten years ago by Bordet.[229] It has been shown in animals[230] and in man[231] that the two antigens exert no mutual interference as judged by laboratory measurements of antibody response. Kendrick[216, 232] and Sauer[233, 234] and their associates carried out field studies in which alum-precipitated combined pertussis vaccine and diphtheria toxoid was used. Both groups found that the mixture gave protection against pertussis and yielded a high proportion of Schick-negative subjects. Lapin[235] and Miller and Saito[212] suggested the addition of tetanus toxoid to the immunization against diphtheria and pertussis, considering various combinations and schedules that could be used with this in view.[212, 236] Lapin concluded that the best results, as judged by laboratory tests, and the fewest reactions were obtained by the administration of the pertussis vaccine alone and the combined toxoids as separate injections either concurrently or later; he[196] noted elsewhere that the triple combination induced a large percentage of severe reactions and alum abscesses. Many physicians have confirmed his observation that the combined irritating effects of pertussis vaccine and alum — perhaps potentiated by the presence of toxoid — tend to produce an undesirably high incidence of local inflammatory reactions and not a few abscesses. Hamilton and Knouf[237] recently reported the use of a fluid triple preparation, with apparently excellent results and few reactions. Such a preparation may offer a satisfactory means of inducing simultaneous immunity to diphtheria, pertussis and tetanus, with a minimum of injections and reactions. Some clinicians, however, preferring to follow Lapin's findings, administer the pertussis vaccine first and the combined toxoids subsequently. This schedule has the advantage of placing the pertussis immunization at the earliest possible date, when it is most needed. Use of triple vaccine-toxoid at this early date has the disadvantage that the infant's response to diphtheria toxoid is likely to be less satisfactory then than it is a few months later.[95]

The use of a booster dose to maintain or restore immunity to pertussis in a previously vaccinated subject has an excellent theoretical basis but has not yet been submitted to any adequate clinical trials. Nevertheless, the antibody responses following booster injections are so striking and so well sustained[238, 239] that there is every reason to believe that the procedure is a valuable one. The analogy with other immunization procedures that have been more thoroughly studied suggests that the response to a booster dose of pertussis vaccine most frequently reaches its peak in ten to fourteen days and is therefore effective in protection just before or perhaps even after actual exposure. On the other hand, primary vaccination against pertussis is of doubtful value during an epidemic or after exposure. Several studies suggest that some degree of protection is obtained even under these circumstances,[196, 240, 241] but such findings are by no means unanimous.[242]

The protection of young infants against pertussis has presented a particular problem, ever since it was shown that the response to vaccination — as with most other immunizations — was less satisfactory in the first than in the second half of the first year of life. Sauer's[243] experience supported this finding and led him to recommend against immunization in the first six months of life. Sako et al.,[244] however, reporting on the immunization of almost 4000 infants less than three months old, observed a communicability rate, in family exposures, of only 19 per cent, in contrast with one of 92 per cent in the control group. Sako's exceptionally good results, which may not be reproducible in a more inclement climate, appear to justify immunization against pertussis at an earlier age than has been customary.

Another attack on this problem is the immunization of pregnant mothers, recommended by Cohen and Scadron,[245] Mishulow et al.[214] and Kendrick and her co-workers.[246] The antibody titers obtained in mothers and transmitted to their infants suggest that some protection is induced by this method.

Typhoid Fever

Evidence of the efficacy of typhoid vaccination is found in several recent reports. Martel[247] describes a localized typhoid epidemic in an outlying district of the Province of Quebec, where the number of

cases fell from 35 in the year before vaccination was begun to 17, 5 and 1 respectively in the succeeding three years. Callender and Luippold,[248] Murphy et al.[249] and Duncan and his associates[250] report outbreaks of typhoid fever among significantly large vaccinated and unvaccinated groups, subject to identical and simultaneous risks of infection, so that the efficiency of the vaccine could be determined. The respective incidence of the disease in each outbreak was as follows: 55 cases among 4000 vaccinated soldiers as against 56 cases among 800 unvaccinated civilians (1.4 vs. 7.0 per cent); 8 cases among 170 vaccinated civilians as against 61 cases among 531 unvaccinated civilians (4.7 vs. 11.5 per cent); and 1 case among 180 vaccinated SPARS as against 17 cases among 194 unvaccinated civilians (0.5 vs. 8.7 per cent).

It is apparent that immunization against typhoid fever — like virtually all other immunizations — affords a marked but not absolute degree of protection. As one would anticipate, numerous reports of typhoid fever in immunized persons have appeared during recent years.[251–254] All reports stress the atypical nature of the disease in immunized persons, and two observers report a relatively high incidence of complications in such cases[252, 254] — a finding that may well be related to the difficulty, and hence the delay, experienced in making the diagnosis.

Gay,[255] almost thirty years ago, wrote:

> It may well be questioned why further modification of typhoid vaccine should seem necessary in view of the extremely good protective results that have already been obtained in certain large groups of individuals . . . . The only answer to such questions is and must ever remain that theoretical considerations based on the understanding of underlying principles will ever precede all practical advances.

Although Smith and Reagh[256] had called attention to the dual nature of certain bacterial agglutinins as long ago as 1903, little attention was paid to this phenomenon until the demonstration of the separate identity of O and H agglutinins by Weil and Felix.[257] Arkwright[258] later demonstrated the close relation between smoothness and virulence of cultures of *Eberthella typhosa*, and their ability to produce O agglutinins and confer protection on guinea pigs through vaccination. Grinnell showed that vaccines prepared from smooth virulent cultures induced bactericidal antibodies[259] and protected mice against lethal quantities of live bacilli[260] to a degree far beyond what could be achieved by vaccination with rough, avirulent cultures. These findings were followed by the studies of Perry and his associates[261] of the Royal Army Medical Corps, and Siler and his co-workers,[262] of the United States Army Medical Corps, as a result of which virulent strains were substituted for the classic Rawlings strain used in vaccine production. The United States Army group[262] subsequently carried out numerous and fundamental studies on methods of evaluating typhoid vaccine.

It is of practical consequence to the physician that these studies and similar investigations elsewhere have provided the basis on which the National Institute of Health four years ago set up minimum requirements for typhoid vaccine entering interstate commerce in the United States.[263] These provide that such vaccines shall be prepared from cultures derived from or antigenically equivalent to the Panama 58 strain of *E. typhosa*, which was selected from among many strains for its high degree of virulence, antigenic composition and immunizing power and which immunizes successfully against strains of *E. typhosa* collected from widely separated parts of the world.[248] The other principal feature of the minimum requirements is a mouse-vaccination test that, although simple to perform, is sufficiently rigid to exclude the poorer grades of vaccine. Griffitts,[264] Luippold[265] Shaffer et al.[266] and others have refined the protection test so that it can be used to distinguish relatively small differences in potency, such as those resulting from minor variations in methods of preparing vaccines. It should be noted that the satisfactory performance of a mouse-protection test for typhoid vaccine depends on the use of the mucin suspension technic[267, 268] and that tests performed without the use of mucin, although of some value, are less easy to interpret; thus the low value that Felix[269] placed on the protection test might have been modified had he employed the mucin technic.

There is no unanimity regarding the best procedure to be employed in the preparation of typhoid vaccine. The classic method is to heat the vaccine at 53 to 56°C. for about sixty minutes and then to add 0.25 per cent Trikresol or an equivalent phenolic preservative. Both heat and phenol are known to be deleterious to many antigens, and a controversy has long existed concerning their effect on typhoid vaccine. Rainsford[270, 271] Siler and his co-workers,[262] Felix,[269] Ungar et al.,[272] Shaffer et al.,[266] Levinson[273] and others employed silver ion, formalin, acetone, chloroform, alcohol, Merthiolate and ultraviolet irradiation for inactivation of the vaccine, the product obtained being in most cases superior in immunizing potency to the classic preparation. Meanwhile, scattered attempts have been made to prepare and evaluate typhoid vaccines modified by the addition of alum[274] or the inclusion of an endotoxoid factor[275, 276]; sufficient data to judge the merits of these modifications are not yet at hand.

The preparation of purified typhoid antigens, free from the extraneous substances present in the whole bacillus, has been the object of numerous investigations and, if accomplished, might aid in the elimination of the untoward side reactions that are the bane of typhoid vaccination. Such an approach must be preceded by a precise definition of the various antigens required for effective immunization and of the role played by each. It was shown some years ago[258] that, of the two classically described O and H antigens, only the former was definitely con-

cerned in protection against typhoid infection. Felix and Pitt[277] described a third antigen, closely associated with virulence and designated by them as the Vi antigen, whose role in protection against infection has not been clearly defined, although it has been shown to possess high immunizing potency in mice.[278, 279] Felix proposed the concept that it stimulated resistance to bacterial invasion, whereas antibodies to the O antigen protected the host against the toxic effect of large quantities of typhoid bacterial substance. This concept has been supported by quantitative studies.[279] Nevertheless, the high efficiency of typhoid vaccines, most of which are prepared in a manner supposed to destroy the delicate Vi antigen, remains to be explained.

Various investigators have prepared relatively pure concentrates of the immunizing antigenic substance of typhoid bacilli.[280–286] Such preparations consist primarily of a complex polysaccharide, with an immunizing potency several thousand times that of the original vaccine, weight for weight. This active substance, which is stable and filterable, appears to be somewhat less toxic, per unit of immunizing potency, than the original vaccine. Treffers[287] recently showed that the toxicity of this substance can be greatly reduced by acetylation with acetic anhydride. Such preparations, because of their inherent advantages, would rapidly become generally used except that, as with chick-embryo smallpox vaccine, they must compete against a product that has been amply proved to be effective against actual clinical infection. It will therefore take a bold spirit to induce the medical or public-health professions to try purified typhoid antigens on a significantly large scale.

The standard dosage of typhoid vaccine — 0.5, 1.0 and 1.0 cc. subcutaneously, usually at intervals of seven to ten days — has scarcely been questioned since its establishment. Bensted[288] advocated diminishing the dosage for civilian immunization, simply to reduce the incidence of side reactions. The ritualistic observance of the usual interval is no longer adhered to, and the United States Army regulations now permit the resumption of an interrupted course of immunization instead of repeating it in its entirety, as was formerly required. Although evidence is lacking, extensive experience with other types of immunization indicates that longer intervals between doses of typhoid vaccine would doubtless give an immunity superior to that obtained with one-week intervals.

Intradermal immunization has had its advocates since it was first proposed by Tuft.[289] Of the numerous subsequent studies of this method,[290–294] all but two[291, 294] evaluated the results only by agglutinin titrations. All observers reported milder reactions following intradermal immunization; Van Gelder and Fisher,[292] who obtained poorer agglutinin titers following intradermal injection, nevertheless considered the reduced reactions sufficient to render the intradermal method superior to the subcutaneous method for typhoid immunization. Tuft[291] and Luippold[294] employed mouse-protection tests for evaluating the results. Their findings conflict, and further studies may be required to determine the usefulness of this method for primary immunization.

Largely because of the theoretical and experimental support that oral antityphoid immunization received from the work of Besredka,[295] this method has been rather widely employed. Recent reports indicated that little, if any, agglutinin formation[296, 297] and no detectable mouse-protective antibodies[262] followed its use. General opinion among immunologists is that the procedure as at present employed is of little value. It is hardly surprising that a report of intranasal typhoid immunization[298] yielded equally negative results.

Reimmunization against typhoid fever, as instituted in the United States Army a generation ago, consisted of a repetition of the initial immunizing course at three-year intervals. In the light of the knowledge of the time, this was a sound procedure. Subsequently, agglutinin studies showed that the antibody response to reimmunization was superior to that following the initial course of vaccine.[299] This was confirmed later by mouse-protection studies,[262] which also demonstrated the correctness of Perry's observation[290] that a single dose of vaccine, either 0.5 cc. subcutaneously or 0.1 cc. intradermally, was sufficient to reawaken a formerly established immunity. Furthermore, it appeared that such a single dose was effective even in persons who had not been revaccinated for a number of years.[300] It is therefore generally recommended that persons who have had one course of primary antityphoid immunization no longer need to repeat a complete course periodically, but may maintain an adequate degree of protection by means of periodic single doses of vaccine, either 0.5 cc. subcutaneously or 0.1 cc. intradermally. The latter procedure apparently is the more effective of the two,[262, 300] but for practical purposes the subcutaneous route is frequently adopted. To maintain a high level of immunity, such single booster doses should be administered annually,[300] but as suggested above, almost all subjects who have had no typhoid immunization for many years show a vigorous antibody response following a single booster dose.

Combined immunization, several antigens being given in a single dose, may be said to have been established with the use of typhoid-paratyphoid A and B vaccine during World War I. Such mixtures were extended, particularly in the British armed forces, to include cholera vaccine, and favorable reports on such multiple combinations have appeared in Germany.[301] Quantitative studies on the comparative immunizing potency of such mixtures of enteric vaccines were made on typhoid-paratyphoid A and B vaccine by Longfellow and Luippold,[302] who observed that it appeared to produce a lower

level of antityphoid immunity than that noted in earlier studies using monovalent typhoid vaccine. Although the two studies are not strictly comparable, the findings suggest that the relative efficacy of the various combinations in current use should be reinvestigated. Several years ago it was suggested, on the basis of United States Army statistics, that immunization with typhoid-paratyphoid A and B vaccine provided some protection not only against the designated infections but also against various milder forms of diarrheal disease.[303] This seems to be a reasonable possibility, in the light of current knowledge of the antigenic structure of the various strains of the paratyphoid group. Longfellow and Luippold,[304, 305] using mouse-protection tests, offered evidence that such protection is directly related to the antigens shared by the organisms. Thus it may be possible, by careful selection of organisms having an appropriate antigenic pattern and quality, to prepare a vaccine providing cross-immunity against a relatively large number of clinically infective strains. Clinical evidence of the efficacy of the paratyphoid components in preventing paratyphoid A or B fevers, however, has not been established on as sound a basis as has been done for typhoid vaccine; Syverton et al.[306] in a recent report on an outbreak of paratyphoid A in military personnel, contributed pertinent observations on this question.

Typhoid or typhoid-paratyphoid vaccines have been combined with diphtheria or tetanus toxoids, or both,[147, 307, 308] with no evidence of loss and some reports of definite increase in effectiveness. Such combinations have practical value for military purposes, and also, in a limited way, for certain civilian needs.

Reactions to typhoid vaccination have always represented a major obstacle to the use of this procedure, especially among civilians. As noted above, Bensted[288] suggested that this difficulty be met by reduction in dosage, but there is no published evidence of the immunizing efficacy of less than the standard doses of the vaccine. Over twenty years ago, following the suggestion of Dr. Béla Johan, of Hungary, the Massachusetts Antitoxin and Vaccine Laboratory effected a definite reduction in the incidence of reactions by centrifuging the crude vaccine, discarding the supernatant and resuspending the sediment in cresolized, buffered saline solution. Two decades later, however, the mouse-protection test showed that such a preparation possessed but a marginal immunizing potency. The method of inactivating the vaccine was revised, Merthiolate being substituted for heat and Trikresol, with a resultant marked increase in potency.[266] No data are yet at hand to determine the comparative reactions produced by the current product. The studies of Morgan[284, 286, 309] and others suggest that chemical separation of the toxic from the antigenic component of typhoid vaccine may be difficult if not impossible; the final solution of the problem may therefore lie in detoxification.[287] Some such change in the fundamental nature of the vaccine must be sought, if it is to receive the general acceptance that must at times be required.

An occasional local reaction is the appearance of a small granulomatous reaction at the site of an intradermal inoculation of the vaccine.[310] Such reactions may be of cosmetic importance in females, but are of little significance otherwise. Various other reactions are ascribed to the vaccine from time to time. The report of Toomey and Tischer,[311] suggesting that typhoid vaccination may increase susceptibility to poliomyelitis, is too limited in scope to be regarded as significant without further study. The risk of inducing so-called "provocative typhoid" by vaccination in the presence of incipient infection was long maintained by some observers, being emphasized by no less an authority than Topley.[312] Fitzgerald's[313] skepticism regarding this phenomenon, however, is shared by many of those experienced in the control of the disease.

(To be concluded)

References

193. Dauer, C. C. Reported whooping cough morbidity and mortality in United States. *Pub. Health Rep.* **58**:661-676, 1943.
194. Editorial. Control of whooping cough. *New Eng. J. Med.* **231**: 718, 1944.
195. Leslie, P. H., and Gardner, A. D. Phases of *Haemophilus pertussis*. *J. Hyg.* **31**:423-434, 1931.
196. Lapin, J. H. *Whooping Cough*. 238 pp. Springfield, Ill.: Charles C Thomas, 1943.
197. Felton, H. M., and Willard, C. Y. Current status of prophylaxis by Hemophilus pertussis vaccine. *J. A. M. A.* **126**:294-299, 1944.
198. Bustamante, M. E. Estudio de la vacuna pertussis en la immunización activa. *Rev. d. Inst. salub. y enferm. trop.* **3**:189-199, 1942.
199. Galvin, L. F., and Wampler, F. J. Study of value of pertussis vaccine. *Virginia M. Monthly* **71**:251, 1944.
200. Garvin, J. A. Efficacy of whooping cough vaccine. *Ohio State M. J.* **41**:229, 1945.
201. Editorial. Vaccination against whooping cough. *Brit. M. J.* **2**: 222, 1945.
202. Bell, J. A. Pertussis prophylaxis with two doses of alum-precipitated vaccine. *Pub. Health Rep.* **56**:1535-1546, 1941.
203. Kendrick, P., and Eldering, G. Study in active immunization against pertussis. *Am. J. Hyg.* **29**:133-153, 1939.
204. Weiss, E. S., and Kendrick, P. L. Effectiveness of pertussis vaccine: application of Sargent and Merrell's method of measurement. *Am. J. Hyg.* **38**:306-309, 1943.
205. Lapin, J. H. Stimulation dose in whooping cough. *J. Pediat.* **20**: 18-25, 1942.
206. Doull, J. A., Shibley, G. S., and McClelland, J. E. Active immunization against whooping cough: interim report of Cleveland experience. *Am. J. Pub. Health* **26**:1097-1105, 1936.
207. Siegel, M., and Goldberger, E. W. Active immunization of tuberculous children against whooping cough with Sauer's vaccine. *J. A. M. A.* **109**:1088-1092, 1937.
208. McFarlan, A. M., Topley, E., and Fisher, M. Trial of whooping-cough vaccine in city and residential nursery groups: report to Medical Research Council. *Brit. M. J.* **2**:205-208, 1945.
209. Toomey, J. A., and Takacs, W. S. Effect of various blood-mediums on growth characteristics of *H. pertussis*. *J. Infect. Dis.* **62**:297-299, 1938.
210. Lapin, J. H., Cohen, P., and Weichsel, M. Prophylactic vaccination against whooping cough. *Arch. Pediat.* **56**:590-598, 1939.
211. Miller, J. J., Jr. Present status of immunization against pertussis. *California & West. Med.* **53**:25-28, 1940.
212. Miller, J. J., Jr., and Saito, T. M. Concurrent immunization against tetanus, diphtheria, and pertussis: comparison of fluid and alum-precipitated toxoids. *J. Pediat.* **21**:31-44, 1942.
213. Coppolino, J. F. Pertussis prophylaxis: clinical study. *J. Pediat.* **21**: 348-352, 1942.
214. Mishulow, L., Leifer, L., Sherwood, C., Schlesinger, S. L., and Berkey, S. R. Pertussis antibodies in pregnant women: protective, agglutinating and complement-fixing antibodies before and after vaccination. *Am. J. Dis. Child.* **64**:608-617, 1942.
215. Harrison, W. T., Franklin, J. P., and Bell, J. A. Prophylactic value of single dose of precipitated pertussis vaccine (preliminary report). *Pub. Health Rep.* **53**:793-796, 1938.
216. Kendrick, P. L. Use of alum-treated pertussis vaccine, and of alum-precipitated combined pertussis vaccine and diphtheria toxoid, for active immunization. *Am. J. Pub. Health* **32**:615-626, 1942.
217. Miller, J. J., Jr., Humber, J. B., and Dowrie, J. O. Immunization with combined diphtheria and tetanus toxoids (aluminum hydroxide absorbed) containing Hemophilus pertussis vaccine. *J. Pediat.* **24**:281-289, 1944.

218. Hornibrook, J. W. Cultivation of phase I *H. pertussis* in semi-synthetic liquid medium. *Pub. Health Rep.* **54**:1847-1851, 1939.
219. Wilson, R. J. Production of phase I pertussis vaccine in casein hydrolysate broth. *Canad. J. Pub. Health* **36**:321-326, 1945.
220. Taylor, E. M., and Farrell, L. Notes on production of phase I pertussis vaccine in fluid medium. *Canad. J. Pub. Health* **36**:326, 1945.
221. Cohen, S. M., and Wheeler, M. W. Pertussis vaccine prepared with phase-I cultures grown in fluid medium. *Am. J. Pub. Health* **36**: 371-376, 1946.
222. Sprunt, D. H., and Martin, D. S. *In vivo* neutralization of pertussis toxin with pertussis antitoxin. *Am. J. Path.* **19**:255, 1943.
223. Ospeck, A. G., and Roberts, M. E. Pertussis antitoxin: its relationship to protection in actively and passively immunized mice and rabbits. *J. Infect. Dis.* **74**:22-31, 1944.
224. Evans, D. G. Protective properties of pertussis antisera in experimental infection. *J. Path & Bact.* **56**:49-54, 1944.
225. Weichsel, M., Katona, N., and Liu, F. Pertussis antitoxin. *Am. J. Dis. Child.* **64**:1-10, 1942.
226. Strean, L. P., and Grant, G. Preparation and properties of *Haemophilus pertussis* endotoxin. *Canad. M. A. J.* **43**:528-531, 1940.
227. Silverthorne, N., Fraser, D. T., and Brown, A. Whooping cough: skin tests. *Canad. M. A. J.* **50**:129, 1944.
228. Cravitz, L., and Cauley, J. H. Pertussis immunization program of Boston Health Department: comparative value of two different antigens. *J. A. M. A.* **129**:539-541, 1945.
229. Bordet, J. A propos du vaccin anticoquelucheux. *Bruxelles-méd.* **16**:503-505, 1936.
230. Schütze, H. Simultaneous immunisation against whooping-cough and diphtheria. *Lancet* **2**:192, 1940.
231. Daughtry-Denmark, L. Whooping cough vaccine. *Am. J. Dis. Child.* **63**:453-466, 1942.
232. Kendrick, P. L. Field study of alum-precipitated combined pertussis vaccine and diphtheria toxoid for active immunization. *Am. J. Hyg.* **38**:192-202, 1943.
233. Sauer, L. W., and Tucker, W. H. Simultaneous administration of diphtheria toxoid and pertussis vaccine in young children. *Am. J. Pub. Health* **32**:385-388, 1942.
234. Sauer, L. W., Tucker, W. H., and Markley, E. Immunity responses to mixtures of diphtheria toxoid and pertussis vaccine. *J. A. M. A.* **125**:949-952, 1944.
235. Lapin, J. H. Combined immunization of infants against diphtheria, tetanus and whooping cough. *Am. J. Dis. Child.* **63**:225-237, 1942.
236. *Idem.* Mixed immunization in infancy and childhood. *J. Pediat.* **22**: 439-451, 1943.
237. Hamilton, P. M., and Knouf, E. G. Combined immunization against diphtheria, tetanus, and pertussis. *J. Pediat.* **25**:236-238, 1944.
238. Miller, J. J., Jr., Silverberg, R. J., Saito, T. M., and Humber, J. B. Agglutinative reaction for Hemophilus pertussis: persistence of agglutinins after vaccine. *J. Pediat.* **22**: 637-643, 1943.
239. Rambar, A. C., Howell, K. M., Denenholz, E. J., Janota, M., and Stanard, R. Studies in immunity to pertussis. II. Effect of stimulating dose of *H. pertussis* vaccine. *Am. J. Dis. Child.* **65**: 730-732, 1943.
240. Davis, H. M. Clinic for diagnosis and prevention of whooping cough. *M. Officer* **66**:173, 1941.
241. Dungal, N., Thoroddsen, S., and Águstsson, H. Vaccination against whooping cough. *J. A. M. A.* **125**:200-202, 1944.
242. Alston, P. Pertussis: vaccine therapy and prophylaxis. *Irish J. M. Sc.* **6**:156-161, 1944.
243. Sauer, L. W. Age factor in active immunization against whooping cough. *Am. J. Path.* **17**:719-723, 1941.
244. Sako, W., Treuting, W. L., Witt, D. B., and Nichamin, S. J. Early immunization against pertussis with alum precipitated vaccine. *J. A. M. A.* **127**:379-384, 1945.
245. Cohen, P., and Scadron, S. J. Placental transmission of protective antibodies against whooping cough by inoculation of pregnant mother. *J. A. M. A.* **121**:656-662, 1943.
246. Kendrick, P., Thompson, M., and Eldering, G. Immunity response of mothers and babies to injections of pertussis vaccine during pregnancy. *Am. J. Dis. Child.* **70**:25-28, 1945.
247. Martel, E. Vaccination against typhoid fever in outlying districts of Quebec. *Canad. Pub. Health J.* **33**:130-133, 1942.
248. Callender, G. R., and Luippold, G. F. Effectiveness of typhoid vaccine prepared by U. S. Army. *J. A. M. A.* **123**:319-321, 1943.
249. Murphy, W. J., Petrie, L. M., and Morris, J. F. Incidence of typhoid fever in population exposed to contaminated industrial water supply. *Indust. Med.* **13**:995-997, 1944.
250. Duncan, T. G., Doull, J. A., Miller, E. R., and Bancroft, H. Outbreak of typhoid fever with orange juice as vehicle, illustrating value of immunization. *Am. J. Pub. Health* **36**:34-36, 1946.
251. Malbin, B. Typhoid fever occurring in immunized persons. *J. A. M. A.* **115**:33-36, 1940.
252. Shtaynshneyder, E. E. Typhoid in vaccinated. *Sovet. med.* (No. 7) **5**:8-10, 1941.
253. Scott, W. I. D. Typhoid infection in inoculated. *J. Roy Nav. M. Serv.* **29**:198-202, 1943.
254. Tullis, J. L. Typhoid in previously immunized subjects: report of seven cases, with discussion of diagnosis, clinical course and complications. *War Med.* **7**:95-99, 1945.
255. Gay, F. P. *Typhoid Fever Considered as a Problem of Scientific Medicine.* 286 pp. New York: Macmillan Company, 1918. P. 163.
256. Smith, T., and Reagh, A. L. Non-identity of agglutinins acting upon flagella and upon body of bacteria. *J. Med. Research* **10**: 89-100, 1903.
257. Weil, E., and Felix, A. Weitere Untersuchung en über das Wesen der Fleckfieberagglutination. *Wien. klin. Wchnschr.* **30**:1509-1511, 1917.
258. Arkwright, J. A. Value of different kinds of antigen in prophylactic "enteric" vaccines. *J. Path. & Bact.* **30**:345-364, 1927.
259. Grinnell, F. B. Study of comparative value of rough and smooth stains of *B. typhosus* in preparation of typhoid vaccines. *J. Immunol.* **19**:457-464, 1930.
260. *Idem.* Study of dissociation of Rawlins strain of *Bacterium typhosum* with special reference to its use in production of antityphoid vaccine. *J. Exper. Med.* **56**:907-918, 1932.
261. Perry, H. M., Findlay, H. T., and Bensted, H. J. Antityphoid inoculation: observations on variation of *Bact. typhosum* in vivo. *J. Roy. Army M. Corps* **61**:81-89, 1933.
262. Siler, J. F., et al. *Immunization to Typhoid Fever: Results obtained in the prevention of typhoid fever in the United States Army, United States Navy, and Civilian Conservation Corps, by the Use of Vaccines.* 276 pp. Baltimore: The Johns Hopkins Press, 1941.
263. National Institute of Health, Bethesda, Maryland. Minimum requirements for typhoid vaccine, July 15, 1942.
264. Griffitts, J. J. Laboratory method of determining potency of typhoid vaccine. *Pub. Health Rep.* **59**:1515-1528, 1944.
265. Luippold, G. F. Proposed typhoid immunogenic unit for evaluation of antityphoid immunizing substances. *Am. J. Pub. Health* **35**:153-158, 1945.
266. Shaffer, M. F., Wetterlow, L. H., and Edsall, G. Preparation of potent "washed" typhoid vaccine. Presented at the Second Wartime Public Health Conference, American Public Health Association, New York City, October 4, 1944.
267. Nungester, W. J., Wolf, A. A., and Jourdonais, L. F. Effects of gastric mucin on virulence of bacteria in intraperitoneal injections in mouse. *Proc. Soc. Exper. Biol. & Med.* **30**:120, 1932.
268. Rake, G. Enhancement of pathogenicity of human typhoid organisms by mucin. *Proc. Soc. Exper. Biol. & Med.* **32**:1523, 1935.
269. Felix, A. New type of typhoid and paratyphoid vaccine. *Brit. M. J.* **1**:391-395, 1941.
270. Rainsford, S. G. Sterilization of T.A.B.C. vaccine. *J. Hyg.* **37**: 539-551, 1937.
271. *Idem.* Further studies on sterilization of T.A.B.C. vaccine. *J. Hyg.* **39**:131-142, 1939.
272. Ungar, J., Jenner, R. M., and Hunwicke, R. F. Observations on preparation and testing of antigenic fractions from *Bact. Typhosum*. *J. Path. & Bact.* **54**:331-340, 1942.
273. Levinson, S. O., Milzer, A., Shaughnessy, H. J., Neal, J. L., and Oppenheimer, F. Production of potent inactivated vaccines with ultraviolet irradiation. II. Abbreviated preliminary report on sterilization of bacteria and immunization with rabies and St. Louis encephalitis vaccines. *J. A. M. A.* **125**:531, 1944.
274. Leon, A. P., Escarza, F., and Rabasa, E. Immunización activa artificial contra las fiebres tifoideas y paratifoideas A y B, con una sola dosis de vacuna T.A.B. precipitada con alumbre: estudios de la respuesta immunológica. *Rev. d. Inst. salub. y enferm. trop.* **2**:161-186, 1941.
275. Grasset, E., and Lewin, W. Production and persistence of H and O agglutinins and complement-fixing bodies in persons inoculated with typhoid endotoxoid vaccine. *Brit. J. Exper. Path.* **17**:179-186, 1936.
276. Lovrekovich, I., and Rauss, K. Schutzimpfung gegen Abdominaltyphus durch die einmalige Injektion eines neuen, präzipitierten Impfstoffes. *Zschr. f. Immunitätsforsch. u. exper. Therap.* **101**: 194-210, 1942.
277. Felix, A., and Pitt, R. M. New antigen of *B. typhosus*: its relation to virulence and to active and passive immunisation. *Lancet* **2**: 186-191, 1934.
278. Luippold, G. F. Antityphoid activity of Vi antigen from extrageneric sources. *Science* **99**:497, 1944.
279. Luippold, G. F. Typhoid vaccine studies. X. Suitability of Vi antigen as auxiliary immunogen for typhoid vaccine. *Am. J. Pub. Health* **36**:15-25, 1946.
280. Felton, L. D., and Wakeman, F. B. Essential immunizing antigen of typhoid bacillus. *Bull. Johns Hopkins Hosp.* **60**:178-191, 1937.
281. Wakeman, F. B. Specific somatic polysaccharide as essential immunizing antigen of typhoid bacillus. *Mil. Surgeon* **84**:318-338 and 452-471, 1939.
282. Palmer, J. W., and Gerlough, T. D. Simple method for preparing antigenic substances from typhoid bacillus. *Science* **92**:155, 1940.
283. Freeman, G. G. Preparation and properties of specific polysaccharide from *Bact. typhosum Tyz. Biochem. J.* **36**:340-355, 1942.
284. Morgan, H. R. Immunologic properties of an antigenic material isolated from *Eberthella typhosa*. *J. Immunol.* **41**:161-180, 1941.
285. Morgan, H. R., Favorite, G. O., and Horneff, J. A. Immunizing potency in man of purified antigenic material isolated from *Eberthella typhosa*. *J. Immunol.* **46**:301-307, 1943.
286. Morgan, H. R. Active immunization with purified antigens of *Eberthella typhosa*, *Salmonella paratyphi*, and *Salmonella schottmuelleri*. *Am. J. Pub. Health* **35**:614-620, 1945.
287. Treffers, H. P. Detoxification of dysentery and typhoid-soluble antigens by chemical means. Presented at forty-sixth general meeting of the Society of American Bacteriologists, Detroit, May 22, 1946. *J. Bact.* **51**:642, 1946. (*Abstr.*)
288. Bensted, H. J. Modern practise in war-time — immunisation of soldiers and civilians: immunisation against bacterial infections. *J. Roy. Inst. Pub. Health & Hyg.* **4**:17-26, 1940.
289. Tuft, L. Active immunization against typhoid fever, with particular reference to intradermal method. *J. Lab. & Clin. Med.* **16**:552-556, 1931.
290. Perry, R. M. Comparison of typhoid "O" and "H" agglutinin responses following intracutaneous and subcutaneous inoculation of typhoid, paratyphoid A and B vaccine. *Am. J. Hyg.* **26**:288-393, 1937.
291. Tuft, L. Further studies of intracutaneous method of typhoid vaccination. *Am. J. M. Sc.* **199**:84-90, 1940.
292. Van Gelder, D. W., and Fisher, S. Intradermal immunization: III. Typhoid fever. *Am. J. Dis. Child.* **62**:933-938, 1941.
293. Kamp, M. Mass typhoid fever immunization — intradermal method. *J. Indiana M. A.* **36**:584, 1943.
294. Luippold, G. F. Typhoid vaccine studies. IX. Intracutaneous versus subcutaneous vaccination for initial immunization. *Am. J. Pub. Health* **34**:1151-1162, 1944.
295. Besredka, A. *Local Immunisation: Specific dressings.* 181 pp. Baltimore: Williams & Wilkins Company, 1927.
296. Naumer, H. A., and Nerb, L. Reactions and agglutinin responses to various methods of typhoid immunization. *Arch. Pediat.* **60**: 63-68, 1943.
297. Elledge, L. C., Kennedy, M. A., and Cumming, K. M. Comparative study of immunity produced in typhoid and associated diseases by subcutaneous and oral vaccinations. *M. Bull. Vet. Admin.* **20**: 56, 1943.
298. Sordelli, A., Manzullo, A., Ferrari, J., and Navarro Viola, R. La aplicación de varios antígenos por vía nasal: estudio experimental. *Rev. d. Inst. bact. Buenos Aires* **12**:134-139, 1943.

299. Feemster, R. F. Effect of typhoid fever and of previous typhoid vaccination on antibody response to inoculation with typhoid vaccine. *J. Infect. Dis.* **50**:121-133, 1932.
300. Longfellow, D., and Luippold, G. F. Typhoid vaccine studies. Revaccination and duration of immunity. *Am. J. Pub. Health* **30**: 1311-1317, 1940.
301. Bartos, D. Die aktive Immunisierung mit Kombinierten Vaccinen. *Deutsche Militärarzt* **5**:321-324, 1940.
302. Longfellow, D., and Luippold, G. F. Immunization to typhoid and paratyphoid fevers. *Am. J. Hyg.* **38**:139-151, 1943.
303. Callender, G. R., and Inmon, E. H. Diarrhea, enteritis, and dysentery. *Army M. Bull.* No. 40. 1937. Pp. 24-75.
304. Luippold, G. F. Typhoid vaccine studies. V. Studies on relationship between antigenic content and immunogenic properties of bacterial suspensions. *Am. J. Hyg.* **36**:354-361, 1942.
305. Longfellow, D., and Luippold, G. F. Typhoid vaccine studies. VI. Production of cross-immunity between members of typhoid-paratyphoid group of micro-organisms. *J. Immunol.* **45**:249-260, 1942.
306. Syverton, J. T., Ching, R. E., Cheever, F. S., and Smith, A. B Typhoid and paratyphoid A in immunized military personnel *J. A. M. A.* **131**:507-514, 1946.
307. Ramon, G., and Zoeller, C. Les "vaccins associés" par union d' une anatoxine et d'un vaccin microbien (TAB) ou par mélanges d'anatoxines. *Compt. rend. Soc. de biol.* **94**:106-109, 1927.
308. Sordelli, A., Sanchez, S., Franzani, O., Ferrari, J. P., and Gvirtzman, I. Vacunación asociada. *Rev. d. Inst. bact., Buenos Aires* **12**: 103-119, 1943.
309. Morgan, H. R. Pathologic changes produced in rabbits by toxic somatic antigen derived from *Eberthella typhosa*. *Am. J. Path.* **19**:135-145, 1943.
310. Tilden, I. L., and Arnold, H. L., Jr. Chronic granuloma following intradermal injection of typhoid vaccine. *Arch. Path.* **36**:13-18, 1943.
311. Toomey, J. A., and Tischer, L. A. Typhoid-paratyphoid vaccine and poliomyelitis. *Am. J. Dis. Child.* **66**:12-15, 1943.
312. Topley, W. W. C. Rôle of active or passive immunisation in control of enteric infection. *Lancet* **1**:181-186, 1938.
313. Fitzgerald, G. Provocative typhoid. *Lancet* **2**:127, 1944.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 32351

PRESENTATION OF CASE

A forty-six-year-old housewife entered the hospital because of abdominal pain.

The patient had had three pregnancies, after each of which she noticed some weakness of the legs and a staggering gait. Seven years before entry, following the last pregnancy and a subsequent panhysterectomy for placenta accreta, these symptoms persisted and gradually progressed. Numbness and paresthesia in the legs, nocturnal back pain and poor sphincter control also developed. The patient was seen at this hospital three years before entry, when neurologic examination revealed slight spasticity of the arms and moderate spasticity of the legs, without paralysis or weakness. She also had a band of hyperesthesia to pinprick from the third to the sixth rib, as well as absent vibratory sense and poor position sense in the lower extremities. The Romberg test was positive. The heel-to-skin test was poorly performed. The deep tendon reflexes were all hyperactive. The plantar reflexes were extensor on both sides, and there was a Hoffmann sign on the left. Physical examination was otherwise negative, except for some resistance to deep palpation and slight tenderness in the right upper quadrant, with a questionable freely movable mass just to the right of and extending from the umbilicus upward to the right costal margin. A diagnosis of multiple sclerosis was made, and the patient was followed in the Out Patient Department. The symptoms continued to increase gradually, and several weeks before entry she began to notice numbness in the hands. During the year before entry a gradual increase in the size of her abdomen, accompanied by occasional vague dragging sensations, had been noticed. Ten days before entry a tight feeling had developed in the abdomen, and the dragging sensations had become painful. Four days later the patient began to have sharp pains in the right lower quadrant every time she exerted herself or moved the abdomen. These pains gradually grew worse, and the entire right side of the abdomen became tender. She also lost her appetite and ate very little, but she did not vomit. During the four days before entry the abdomen had shown a sudden further increase in size until she was unable to button her coat. She had had normal bowel movements every day, including the day of admission.

Physical examination revealed a somewhat pale woman in moderate distress. The heart and lungs were normal. A large irregular, elongated tender mass filled the entire right side of the abdomen from the costal margin to the pelvic brim. It was not possible to feel between this mass and the liver at the right costal margin. The mass appeared to move with respiration. Peristalsis was present. Vaginal examination revealed a small freely movable, slightly tender cervical stump. The neurologic findings were essentially similar to those of the previous examination, with a slight progression.

The temperature was 101°F., the pulse 88, and the respirations 18. The blood pressure was 128 systolic, 78 diastolic.

Examination of the blood revealed a hemoglobin of 12 gm. and a white-cell count of 10,600, with 84 per cent neutrophils. The urine was normal.

A plain film of the abdomen revealed a considerable amount of gas and fecal material in the large bowel, particularly in one isolated loop lying in the midabdomen (Fig. 1). There was an ill-defined soft-tissue mass in the right lower abdomen. In the standing position no air was seen under the diaphragm, and no fluid levels were visible within the bowel loops.

An operation was performed on the second hospital day.

Differential Diagnosis

Dr. Franklin G. Balch, Jr.: May we see the x-ray films?

Dr. James R. Lingley: In all the films there is a great deal of gas in the colon and the dilated loop mentioned in the record looks like an enormously distended, dilated and inverted cecum. The mass is questionable, although there is increased density in that region. One might explain the dilatation of the cecum by the mass obstructing the ascending colon.

Dr. Balch: This is essentially the problem of a forty-six-year-old woman with a definite diagnosis of multiple sclerosis and a right-sided abdominal mass. I cannot in any way connect the mass in the right side with the diagnosis of multiple sclerosis, and the nature of the right-sided mass must therefore be explained. Seven years before admission a panhysterectomy had been performed. According to my ideas, a panhysterectomy is a total hysterectomy, including the uterus, both ovaries and tubes. Later in the physical examination, however, the cervix is mentioned, and I wonder whether the ovaries were removed.

Figure 1. *Plain Film of Abdomen.*

Dr. W. P. Giddings: We were told that the ovaries had been removed.

Dr. Balch: Under those circumstances an ovarian cyst can be excluded. That is the likeliest diagnosis for a tumor in the right side, except that it extended up to the costal margin.

Localized ascites is unusual, and I do not entertain that diagnosis seriously.

Diseases of the liver and gall bladder must be considered. It was stated in the record that the examiner could not palpate between the liver and the mass. That does not mean that the mass necessarily arose from the liver. Echinococcal cyst in the liver is a possibility, but no mention is made about where the patient had lived and no echinococcal complement-fixation test was done, so that the data are insufficient to warrant that diagnosis.

There is a possibility that hydrops of the gall bladder was present, but the history is too long and drawn out for such a diagnosis. If the statement is correct, and I assume that it is, the patient noticed a gradual increase in the size of the abdomen for a year. The same objection holds true for empyema of the gall bladder. Furthermore, she was not sick enough for an empyema and the pain was in the right lower quadrant and not the right upper quadrant, as one would expect with gallbladder disease, which I believe can be ruled out.

What other form of cyst or tumor could this have been? A solitary cyst of the lower pole of the kidney is a possibility. The x-ray studies do not suggest it, although sufficient gas was present to obscure such a lesion. No investigation was made of this possibility, and I expect that such a lesion would have been felt on physical examination. Cyst of the pancreas occurs higher up and is closer to the midline. That diagnosis is therefore unlikely.

The history certainly does not suggest an intrinsic bowel lesion, such as intestinal obstruction. The bowel movements were normal up to the day of admission, and the pains were not typical of intestinal obstruction. The x-ray films are quite confusing, because I cannot figure out, if the cecum was dilated to that extent, why there were no symptoms of obstruction. There was probably subacute obstruction.

Cyst of the omentum, which is a rare lesion, is another possibility, but it would not account for the x-ray findings.

I am inclined to believe that a mesenteric cyst fits the picture better than any other single diagnosis. The symptoms persisted for a long time, and mesenteric cyst, of course, grows to large proportions. To be sure, such a lesion is usually not confined to the right side, but adhesions from the previous operation could have prevented the tumor mass from extending over to the left side and could also explain the enlargement. Bleeding into the cyst would account for the increase in the size of the cyst a few days before entry. I cannot make a positive diagnosis, but my guess is that this woman had a mesenteric cyst possibly causing partial obstruction.

DR. LINGLEY: Was the mass hard or soft?

DR. GIDDINGS: It was fairly firm; it appeared in part to be tympanitic.

DR. LINGLEY: I wonder if the mass felt three years previously could possibly have been the cecum — an anatomic variation of the cecum that had become twisted.

DR. BENJAMIN CASTLEMAN: Do you mean a volvulus of the cecum?

DR. LINGLEY: Yes.

DR. CASTLEMAN: Dr. Giddings, would you give us your impression of the case?

DR. GIDDINGS: We were as confused as Dr. Balch. We knew that the ovaries and the appendix had been removed. We entertained many of the diagnoses that Dr. Balch has mentioned, namely, mesenteric cyst, retroperitoneal cyst and tumor. On the basis of the x-ray evidence we were led to favor a diagnosis of volvulus of either the sigmoid or the cecum.

CLINICAL DIAGNOSIS

Volvulus of sigmoid or cecum.

DR. BALCH'S DIAGNOSIS

Mesenteric cyst.

ANATOMICAL DIAGNOSES

Acute and chronic cholecystitis, with hydrops, producing partial obstruction of cecum.

Cholelithiasis.

PATHOLOGICAL DISCUSSION

DR. GIDDINGS: At operation the diagnosis was immediately apparent. In the abdomen an enormously distended gall bladder, 18 cm. long and 10 to 13 cm. in diameter, extending to the crest of the ilium, was found. It was acutely inflamed and markedly thickened, and there was an adhesion between the gall bladder and the cecum, with apparently partial obstruction and distortion of the cecum to produce the x-ray picture. With removal of the gall bladder the cecum fell back to its normal position.

DR. CASTLEMAN: Can the gall bladder be seen on this film?

DR. LINGLEY: The mass described in the record was probably the gall bladder.

DR. CASTLEMAN: Is it not too low?

DR. GIDDINGS: I think that the mass was a little too far forward on the left for the gall bladder.

DR. CASTLEMAN: The gall bladder we received was enormous; it was fully distended, with marked inflammation, both acute and chronic. A stone impacted in the ampulla had caused the marked distention.

CASE 32352

PRESENTATION OF CASE

A seventy-four-year-old housewife entered the hospital because of abdominal pain.

For two years before entry the patient had had intermittent attacks of sharp periumbilical pain

lasting from several hours to several days. Ten days before entry she began to have a particularly severe attack and vomited some whitish material. Because the pain continued she went to bed, where she remained until admission. Seven days before entry she had had several loose bowel movements, but thereafter the stools were brown and normally formed. On the day of admission the patient felt unusually weak, sweaty and nauseated. She vomited several times, producing some whitish material. The periumbilical pain was also severer but was relieved by codeine. When she was seen that night she had been free of pain for about three hours. There had been no hematemesis, melena, fever, chills or upper respiratory infection.

The appendix and one ovary had been removed at the age of twenty-nine.

Physical examination revealed a poorly nourished woman with cold extremities and livid mottling over the chest and abdomen. The pupils were small and reacted poorly to light. The heart sounds were weak but otherwise of good quality. The heart rate was 96. Fine inspiratory rales were heard at both lung bases. The abdomen was soft and nontender. Peristalsis was somewhat hyperactive. No masses could be felt. Pelvic examination was negative except for a slight prolapse, with cystocele and rectocele.

The temperature was 99°F., and the respirations 18. The pulse and blood pressure were unobtainable.

Examination of the blood revealed a red-cell count of 6,400,000, with 60 per cent hemoglobin, and a white-cell count of 20,000.

The patient was anuric on admission, and no urine was found in the bladder. A small specimen obtained on the following day gave a + test for albumin, and the sediment contained 5 to 10 white cells per high-power field. A culture grew abundant nonhemolytic streptococci. A glove specimen of stool was guaiac negative.

Soon after entry the patient vomited about 150 cc. of dark-red material, which gave a ++++ guaiac test. She was given plasma, 5 per cent dextrose in saline and adrenocortical extract. After about three hours of intravenous therapy the blood pressure was 78 systolic, 0 diastolic. A white-cell count done seven hours after entry was 37,400, with 99 per cent neutrophils, and the red-cell count was 6,870,000. Intravenous and intramuscular penicillin was started. Nevertheless the patient gradually lapsed into coma, from which she could be aroused only by painful stimuli.

On the morning after admission the abdomen was noted to be somewhat distended and doughy. Deep pressure in any quadrant caused the patient to cry out. Below the umbilicus in the midline there was a suggestion of a soft mass that did not pulsate. Peristalsis was less active than previously.

Further blood studies revealed a nonprotein nitrogen of 48 mg. per 100 cc. and a serum amylase of 50 units. A lumbar puncture and examination of the spinal fluid were negative. A plain film of the abdomen showed gas-filled, dilated loops of small bowel in the midabdomen, which appeared to be jejunum or upper ileum. There was also a considerable quantity of gas in the transverse colon but little distal to the splenic flexure. The loops of small bowel were spread from one another, suggesting the presence of free fluid. A film of the chest was unsatisfactory because of motion but showed a large area of hazy, homogeneous density at the left base.

Toward evening of the second hospital day respirations became gasping in quality. The abdomen had become resistant and was still tender to palpation. A Miller–Abbott tube drained 500 cc. of chocolate-brown, guaiac-positive liquid with a fecal odor. Gradually the patient's breathing became progressively shallower, and the blood pressure again fell, despite continuous intravenous fluids.

The patient expired thirty hours after admission.

Differential Diagnosis

Dr. Edward Hamlin, Jr.: May we see the x-ray films?

Dr. James R. Lingley: These films are of rather poor quality but show gas in both the colon and the small bowel.

Dr. Hamlin: Can the gas in the colon be traced from the cecum?

Dr. Lingley: Only around to the region of the splenic flexure; from there on there is extremely little gas. This film of the chest shows a great deal of motion, but there is definite consolidation of the left base.

Dr. Hamlin: The one post-mortem finding that I am sure of is bronchopneumonia, but presumably there was something else.

I have been unable, in reading this abstract, to form any satisfactory diagnosis that fits all the criteria. The impression is given that this type of pain existed intermittently for two years, and it becomes difficult to explain this particular attack, which occurred for ten days but with no great change until the very end. The patient had had several loose bowel movements, but the stools were brown and normally formed. Does that mean that she continued to have bowel movements up to entry? I am trying to find out whether there is any question of intestinal obstruction. The question is raised by the x-ray findings to a certain extent, and there are sufficient other factors to make one think of obstruction, although the history is not particularly suggestive. At entry she was obviously in shock. The description of the abdomen is somewhat difficult to interpret, but I gather that the examination was completely negative. Is that correct?

Dr. Donald S. King: This woman was a patient on the Medical Ward on which I was visiting. I

saw her only once on the morning after she was studied in the Emergency Ward. She had entered the hospital in shock, and had been observed by the physicians on various services, including one of the surgical services. At the time I saw her I was told that examination of the abdomen had been absolutely negative on the night of admission.

DR. HAMLIN: She was also obviously dehydrated.

The next thing that interests me is the fact that guaiac-positive material was found in the vomitus but not in the stools, which again implies some degree of obstruction. The white-cell count, which was remarkably high for a seventy-four-year-old woman, despite dehydration, makes one think of infarction. The record on the next morning gives a good description of general peritonitis.

The serum amylase was taken presumably for the question of pancreatitis. In this hospital the serum amylase of 40 units is roughly the top side of normal, so that a serum amylase of 50 is slightly above normal and not particularly helpful.

In summary, this was a disease of relatively long duration that produced an intra-abdominal catastrophe terminally and that caused shock and presumably peritonitis. One might infer that the patient ruptured a hollow viscus and died with, of course, bronchopneumonia. If these assumptions are correct, it might be well to consider the possible hollow viscus that could perforate. The first thing to think of is the bowel, and that brings up the question whether it was the small or large bowel; there are points that lead one to suspect either. The fact that guaiac-positive material was vomited soon after entry makes one believe that possibly this was a relatively high lesion. On the other hand, there is meager x-ray evidence in that direction, and I am unable to call this purely intestinal obstruction, since a negative abdominal examination is unlikely after ten days of obstruction.

Could the gall bladder have perforated? That would explain the long history. Perforation would also explain many of the features and, particularly if it were associated with pancreatitis, could produce shock, but there is nothing in the history to lead one to think of gall-bladder disease in any form. So for lack of corroborative evidence I drop that possibility, which brings me back to the question of bowel.

The obvious lesions that produce a long history such as this patient had are chronic intussusception and chronic volvulus, but they would produce more evidence of obstruction terminally and it is difficult for me to believe that such obstruction was present. I can think of no tumor of the bowel of long duration that causes such a shock-like picture, particularly if the question of blood within the lumen of the bowel is considered, and I have an idea that something is going to turn up to make me feel extremely embarrassed. That brings us to what seems to me the most probable disease, which fulfills most of the criteria but still leaves something to be desired, namely, mesenteric thrombosis. How it could have occurred intermittently for two years I cannot explain, nor do I think it did; but it explains the essentially normal abdomen on entry and also the rupture of the bowel, as the terminal event.

DR. J. W. EWELL: I should like to raise the possibility of carcinoma of the bowel, with perforation.

DR. HAMLIN: I tried to bring in tumor of varying sorts, but I find myself unable to explain how a tumor could have caused shock without peritonitis.

DR. KING: That also bothered me. When I saw the patient she was practically unconscious. We went over the list of possible causes of shock supposedly from an abdominal condition, and put mesenteric thrombosis high on the list. My own guess, which was wrong, was acute pancreatitis, but the trouble with that diagnosis was that it did not explain satisfactorily the symptoms of two years' duration. It is true that when I examined the patient I did not believe that the abdomen was normal. There was some distention, and even though she was almost in coma there seemed to be some tenderness.

CLINICAL DIAGNOSIS

Acute pancreatitis.

DR. HAMLIN'S DIAGNOSES

Mesenteric thrombosis.
Bronchopneumonia.

ANATOMICAL DIAGNOSES

Strangulated small intestine due to an adhesive band.
Hiatus hernia.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: The abdomen contained 500 cc. of hemorrhagic fluid, and an adhesive band, about 1 cm. thick, extended from the under surface of the laparotomy scar to a loop of terminal ileum about 6 cm. proximal to the ileocecal valve. Almost the entire ileum, which was gangrenous, was strangulated by this band.

The lesion in the left lower-lung field was not bronchopneumonia. It was a hiatus hernia containing a part of the stomach and intestines and causing collapse of the left lower lobe.

DR. HAMLIN: This case serves again to point out that intestinal obstruction, even without strangulation, does not always present the classic signs and symptoms.

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POSTWAR WORLD

The postwar world, to date, has been a world of mutual distrust, jealousy and suspicion. It has been a world of unrest, of strife, of disharmony, of violence, of muscle-bulging. We are learning again, as we have learned before and forgotten, that alliance in a common cause does not mean even temporary friendship. The emotional factor of good will is a personal, not a group, phenomenon, and rarely is the moral discipline of the individual sufficient to place good will above immediate self-interest.

The Four Freedoms, around which the allied nations rallied in the dark war days, have been kicked into a cocked hat by some of their adherents and allowed to remain there by the rest. Poland is again bringing to perfection her peculiar art of the pogrom. Mikhailovitch, whom many still suspect of having been one of Yugoslavia's great patriots, has been eliminated by due process of postwar law; on the other hand Bolivia's dictator, after a man hunt through his palace, was recently liquidated and hanged *in corpore delicti*.

Palestine, which gave us one of our early examples of man's violent reactions to a policy of good will toward man, still furnishes us with illustrations of violent reactions. Trieste, that gem of the Adriatic, is again the victim of a snatching contest. China is being spun like a top by her various factions, and Madame Sun Yat-sen, perhaps with some justice, wants the Americans out; Manchuria has apparently been thoroughly looted by our hearty former co-belligerents, the genial Russians, of whom it is currently said, however, that the marshals who won the war are being looked on coldly by the big boss.

Nature has done her best to add to mankind's confusion by providing two years of almost unprecedented crop failures over much of the world, and economic unrest at home seems to be accompanied by that strawberry shortcake of modern journalism — an outbreak of private slaughter, mayhem and rape. Congress, moreover, according to present indications, seems of a mind to preserve the Nation's health by right of eminent domain.

Our domestic problems we will no doubt stagger along with and settle in the usual bivalent democratic fashion — partly right and partly wrong. So far as our foreign relations are concerned, Brooks Atkinson, the able *New York Times* correspondent recently returned from Russia, has given probably the best picture of the working policy toward its neighbors of the bear that walks erect. It might be phrased in the words of the mate of the whaler *Mozambique* to his skipper: "All I wants from you is ceevility and d—— little of that!"

We now know that Russia is bent on fulfilling her own destiny and believes that destiny to be incompatible with the rights of other nations. Her government has not learned — perhaps cannot learn — the lesson of compromise and cannot understand that various political ideologies may exist side by side in the same world. Much may be expected eventually of the Russian people, when

political education is allowed to come their way. Meanwhile Democracy must stand its ground. It has paid too much for what it has won to give up any of its ideals.

"BE NOT THE FIRST"

THE physician who has under his care a patient with Hodgkin's disease, leukemia or some allied disorder is not infrequently confronted with the difficult task of persuading the family, in its desperation, not to cast about for some alleged cure of the disease rather than to adhere to the more conventional forms of therapy proved by experience to be beneficial. This desire on the part of the family is easy to understand; for, on the one hand, the physician in charge must, of necessity, point out the almost certain fatal outcome, and on the other, the layman is quick to grasp at straws and all too ready to believe rumors of true cures by some new and mysterious substance. This is particularly true when the patient has relatives who are scientists yet not physicians. The situation is made even more difficult when the lay press publishes premature and distorted accounts of purely experimental measures or when a physician, in an unguarded moment, speaks of a cure when, in actuality, he is referring to a therapeutic measure under trial that, at the moment, appears to offer some promise.

Twice within the past year the writer of this editorial has been told by medical students that a cure for one or another of these malignant or pseudomalignant conditions has been found. Similar word has also come to the ears of families some member of which has been stricken with one of these dread diseases. Thus is false hope raised that serves only to heighten the distress when failure eventually becomes apparent. It is probably safe to say that any doctor thoroughly familiar with these conditions is aware of what experimental work is being carried out, and it is also probably safe to say that once a true cure has been found or a real therapeutic advance has been made by competent observers this knowledge will not be long in reaching those interested in the field and, indeed, the medical public at large. Concise official statements from competent investigators may be expected as soon as they are justified.

Such a statement has recently been made by Rhoads[1] regarding the use of the nitrogen mustards in leukemia, Hodgkin's disease and certain types of cancer. From this report it is clear that both the "bis" and the "tris" compounds have definite therapeutic limitations and that, broadly speaking, these substances do not constitute a cure or even a great advance over the more conventional x-ray treatment. Toxic effects, including leukopenia, anemia and bleeding tendencies, were encountered, and in some cases the hematopoietic injury exceeded the effect on the tumor. Such remissions as were achieved seldom lasted more than several months. Lymphosarcoma did not respond to these agents any better than it does to x-ray, and acute leukemia was not benefited. It is stated that chronic leukemia is still best handled by appropriate radiation, and early, localized tumors, by radical excision or local radiation. It is concluded that "the experimental use of the nitrogen mustards in the treatment of any active, extensive, neoplastic process is probably justified if other methods of control have proved to be without benefit."

In a somewhat similar vein there is a report from England on the use of urethane in leukemia.[2] Thirty-two cases were treated, and in most there was a marked drop in the white-cell count, a reversal of the differential to more nearly normal and a rise of the red-cell count, but again the beneficial results were temporary and there were toxic manifestations. The authors conclude that there is "no indication that permanent benefit may result from the use of urethane in either myeloid or lymphatic leukemia."

These reports are not encouraging, but they are extremely valuable, since they place in the hands of the attending physician the knowledge that the conventional form of therapy, whether it be radiation or surgery or both, is still best in the hands of competent men, and since they form a firm basis on which to base a reluctance or even a refusal to permit such therapeutic measures to be used in the average case of neoplastic or pseudoneoplastic disease.

REFERENCES

1. Rhoads, C. P. Nitrogen mustards in treatment of neoplastic disease. *J. A. M. A.* **131**:656-658, 1946.
2. Patterson, E., Haddow, A., Thomas, I., and Watkinson, M. Leukemia treated with urethane compared with x-ray therapy. *Lancet* **2**:677-682, 1946.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

BUSSEY — Floyd H. Bussey, M.D., of New Bedford, died May 1. He was in his sixty-second year.

Dr. Bussey received his degree from the University of Michigan Homeopathic Medical School in 1910. He was a fellow of the American Medical Association.

COLLINS — Richard Collins, M.D., of Waltham, died July 28. He was in his seventy-second year.

Dr. Collins received his degree from Harvard Medical School in 1900. He was a member of the staff of the Waltham Hospital, a member of the American College of Surgeons and a fellow of the American Medical Association.

His widow, a son and a daughter survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

POSTPONEMENT OF ELECTIVE TONSILLECTOMY

The Department of Public Health again feels it necessary to advise against elective tonsillectomy during the poliomyelitis season. This constitutes one of the few effective measures that can be taken to minimize the serious effects of poliomyelitis. Although the incidence of the disease is not so high this summer as it was last year, cases are occurring regularly and it is significant that a history of antecedent tonsillectomy was given in three cases, two of which had bulbar paralysis.

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR JULY, 1946

RÉSUMÉ

DISEASES	JULY 1946	JULY 1945	SEVEN-YEAR MEDIAN
Anterior poliomyelitis	11	33	5
Chancroid	2	2	*
Chicken pox	516	363	400
Diphtheria	34	13	13
Dog bite	1372	1229	1227
Dysentery, bacillary	5	44	23
German measles	134	62	62
Gonorrhea	447	537	356
Granuloma inguinale	1	1	*
Lymphogranuloma venereum	2	4	*
Malaria	39	136	1
Measles	2533	735	1159
Meningitis, meningococcal	4	13	13
Meningitis, Pfeiffer-bacillus	1	2	2
Meningitis, pneumococcal	7	3	3†
Meningitis, staphylococcal	0	0	0†
Meningitis, streptococcal	0	0	0†
Meningitis, other forms	0	1	2†
Meningitis, undetermined	7	0	4†
Mumps	216	686	434
Pneumonia, lobar	70	112	112
Salmonella infections	14	8	9
Scarlet fever	183	263	241
Syphilis	486	321	388
Tuberculosis, pulmonary	278	275	255
Tuberculosis, other forms	13	11	18
Typhoid fever	7	0	4
Undulant fever	10	3	4
Whooping cough	564	587	521

*Made reportable December, 1943.

†Four-year average.

COMMENT

Diseases reported at an incidence above the seven-year median included chicken pox, German measles, measles, typhoid fever and whooping cough.

Although anterior poliomyelitis was reported at a figure above the median prevalence, there is no evidence at present that this disease will reach epidemic proportions this year.

Diphtheria was reported at the highest figure for the month of July in the past ten years. This was also true for the months of May and June.

Diseases reported below the median prevalence included bacillary dysentery, meningococcal meningitis, mumps and scarlet fever.

Lobar pneumonia was again at a record low for the sixth consecutive month.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Anterior poliomyelitis was reported from: Arlington, 2; Boston, 1; Cambridge, 1; Falmouth, 1; Marblehead, 1; Medford, 1; Washington, 4; total, 11.

Diphtheria was reported from: Boston, 6; Cambridge, 1; Chelmsford, 1; Everett, 1; Framingham, 2; Gloucester, 7; Lowell, 2; Lynn, 1; Newton, 2; Somerville, 2; Taunton, 6; Worcester, 3; total, 34.

Dysentery, bacillary, was reported from: Boston, 1; Worcester, 4; total, 5.

Encephalitis, infectious, was reported from: Southbridge, 1; total, 1.

Malaria was reported from: Arlington, 1; Attleboro, 1; Boston, 14; Bourne, 1; Cambridge, 2; Georgetown, 1; Haverhill, 2; Hingham, 1; Longmeadow, 1; Lynn, 2; Medford, 1; Newton, 1; North Andover, 1; Peabody, 1; Rockport, 1; Salem, 1; Shrewsbury, 1; Townsend, 1; Waltham, 1; Winchester, 1; Worcester, 3; total, 39.

Meningitis, meningococcal, was reported from: Boston, 2; Fitchburg, 1; Holyoke, 1; total, 4.

Meningitis, Pfeiffer-bacillus, was reported from: Boston, 2; total, 2.

Meningitis, pneumococcal, was reported from: Amherst, 1; Belmont, 1; Boston, 3; Fitchburg, 1; Malden, 1; total, 7.

Meningitis, undetermined, was reported from: Brookline, 2; Cambridge, 1; Millbury, 1; Newton, 1; Plymouth, 1; Worcester, 1; total, 7.

Salmonella infections were reported from: Belmont, 1; Bernardston, 1; Boylston, 1; Cambridge, 1; Falmouth, 1; Lawrence, 2; Lowell, 1; Newburyport, 1; Newton, 1; Northampton, 1; Templeton, 1; Waltham, 1; Worcester, 1; total, 14.

Septic sore throat was reported from: Boston, 5; Foxboro, 1; Greenfield, 1; Quincy, 1; total, 8.

Trichinosis was reported from: Boston, 1; Cambridge, 2; total, 3.

Typhoid fever was reported from: Andover, 1; Arlington, 1; Boston, 1; Chelsea, 1; Somerville, 1; Springfield, 1; Worcester, 1; total, 7.

Undulant fever was reported from: Adams, 2; Carlisle, 1; Dalton, 1; E. Bridgewater, 1; Groveland, 1; Hinsdale, 1; Taunton, 1; Templeton, 1; West Springfield, 1; Westfield, 1; Worcester, 1; total, 12.

MISCELLANY

THE SIGNING OUT OF TUBERCULOUS PATIENTS

When the private physician makes a diagnosis of tuberculosis and succeeds in getting a patient under sanatorium care, he is apt to feel that his job is done. If that patient leaves the sanatorium prematurely, his physician will be handicapped in his subsequent efforts by the failure of this first hospital experience. A knowledge of some of the factors that lead tuberculous patients to leave hospitals against medical advice should help physicians to prepare patients for accepting and completing hospital care. The matter is discussed in a paper, "The Signing Out of Tuberculous Patients," by Jean Berman and Leo H. Berman, which appeared in the April, 1944, issue of *The Family*.

* * *

Those who are interested in helping a patient to use the medical care necessary for recovery and to accept a possible physical limitation, find challenging problems in work with the tuberculous. The importance of this may be realized when hospitals in different parts of the country report that from 22 to 65 per cent of their patients leave A.O.R. ("at own risk").

The patients who refuse all treatment have not been considered. The focus has been on patients who have evinced a desire to get well but who during the course of treatment attempted to terminate their recovery process. All hospital personnel, including the social worker, must accept "It is never

the body only which is out of health, but always the complete being." Often the reasons for leaving the hospital are obscure and great skill is needed to help the patient to be realistic and to direct himself toward the goal of complete recovery.

The treatment and hospitalization of patients with tuberculosis involves months or years of restricted activity. A young athletic boy, suddenly faced with tuberculosis, may revolt at accepting this state. Since the tubercle bacilli carry on their destructive work insidiously, the patient, after he has regained some strength, will insist that his cure is completed. This view is maintained despite the contrary evidence of x-ray and sputum reports. Perhaps the fear of the disease is so great as to cause the patient to reject its reality.

The older man and woman, accustomed to years of labor in factory and home, may also find it difficult to accept the new role of inactivity and dependency. Experience has not fitted them to fill the passing empty hours. The thought of lying quietly in bed while the world hurries on is untenable, and they are tortured by the desire to be back among the working multitudes.

This boredom is more readily conquered by patients accustomed to study or reading, or those who are fortunate enough to have a hobby. Hospitalization is a difficult experience for the majority, but it can be a constructive one. Rarely does a patient who has found activities that lead to growth and development, sign out against advice. There is also a distinct difference between those patients who have made their adjustment and those who have succumbed to the sheltered life of the hospital and have regressed to an infantile, dependent level.

There does not appear to be any constant point at which a patient may feel that the hospital is no longer bearable. Even when he may be apparently adjusted to the hospital routine, the inactivity may lead to cumulative effects until a breaking point is reached. A little supportive treatment at this time will often tide the patient over the rough spot.

A patient entering a hospital brings with him the sum total of his life experiences. He has certain ties, certain obligations, and these remain though they are altered by the new experience. Early contact with the patient and his family can give clues to the patient's motivations and the part the family will play. The marital strengths, the interfamily ties and strains, the relationship in a changing setting should all be weighed and evaluated with the patient. The patient must, if possible, be spared the worry and anxiety of the family. This cannot be done by simply hiding or ignoring real problems. If the family is aware of this, they can show the patient their strengths in meeting problems and assure him that they can keep their balance.

The social worker is often faced with a recently admitted patient who demands to leave the hospital with or without the doctor's permission. An interview usually begins with the patient demanding, "How can I remain here while my family starves?" The social worker can be of invaluable aid in directing the family to sources of help and thus make it possible for the patient to accept his hospital stay knowing that his family will not starve or go homeless.

Life in a hospital is complex. A patient is faced with the need to adjust to his companions, the doctors, the nurses and other personnel. He has to give up practically all his privacy, both physical and mental. There are new ideas to be adjusted to in this microcosm of all nations and races. It is not difficult for friction to arise between the patient and a particular person or routine. Personalities may clash and the sick person may feel that the only solution lies in leaving the hospital. Sometimes the patient does not indicate the real reason for signing out but gives the usual statement that he "can do just as well at home." Other patients are quite verbose regarding the sources of annoyance.

All members of the hospital team can play very important parts in helping the patient adjust not only to his illness but to the hospital life. A healthy adjustment in the hospital implies a psychologic awareness and acceptance of the illness. When the acceptance has not been achieved, the patient rejects the hospital as a symbol of the disease. In the adjustment of the patient to the hospital one factor that might be given special attention is the food. Tuberculous patients are very conscious of the role of food in their cure and of the variations in their weight. This is one of the chief topics of conversation. One director of a sanatorium when asked how he kept down his A.O.R. discharges to a surprisingly low figure replied that he gave the patients the type of food they would get in their own homes.

An analysis cannot give all the reasons why patients interrupt the treatment process. The individuality of every situation is marked, and therein lies the challenge. The problem is a big one. There has been a constant war against tuberculosis. In its earlier stages this fight was on a mechanical level of cleaning up slums, taking mass x-rays or providing the proper type of hospital care. But now we have come to realize that we are dealing with human beings and the control of the disease will come only when the sick person is prepared to participate. — Reprinted from *Tuberculosis Abstracts*, August, 1946.

CORRESPONDENCE

CESAREAN SECTION VERSUS TEST OF LABOR

To the Editor: In his paper appearing in the June 27 issue of the *Journal* Dr. Waters, in discussing fetopelvic disproportion in the borderline pelvis, states: "We frankly admit our inability in many such cases to decide in advance of an adequate test of labor the ability of the patient to deliver herself or to be safely delivered by vagina. We marvel at the judgment and experience of the omniscient, which permit *in advance of labor* appreciation of the size, shape and moldability of the fetal head, the extent of the physiological relaxation of the pelvic joints, the thickness and tension of the nonosseous pelvic structures, the character and effectiveness of the uterine contractions, the time factor in even partial dilatation and effacement of the cervix. . . ." This represents at once an admirable candor and a great waste of wonder. It poses numerous questions.

What is obvious fetopelvic disproportion? Is it invariably concomitant with contracted pelvis borderline or otherwise? What is an "adequate test of labor"? Who are those who possess such judgment and experience that in advance of labor they appreciate the factors listed by Dr. Waters? Where does he find the names or writings of those termed "omniscient"? When and where have they stated that they possess in advance of labor the fundamental obstetric information suggested by Dr. Waters? Will he tear away the veil of anonymity?

It is no omniscence which we bring to our opposition to test or trial of labor. It is rather a profoundly felt resentment of our own ignorance coupled with the fact that we have learned that an adequate test of labor is no cheap commodity. It has no fixed or predictable price. All too often obstetricians are faced with the problem posed by Dr. Waters. All too often, despite all available data, including accurate clinical and x-ray mensuration and the excellent procedure of Hillis, we do not know in advance of labor whether or not the presenting vertex will enter the pelvis. Faced with our own ignorance we have available for the solution of the problem two procedures each necessarily a mere reflection of that ignorance. One may proceed to elective section or to adequate test of labor. Our choice is elective section because we know what it costs.

What is the price of section? The mortality for elective section of the lower segment type is 0.5 per cent.

What exaction is made for a test of labor? Perhaps none. Perhaps twenty-four to ninety-six hours of irregular, purposeless, inefficient pain with the patient undelivered, exhausted and infected, at the end of such time — a major surgical risk. Perhaps a long labor with a badly battered or dead baby as a reward. Perhaps a long labor terminated by a technically and physically difficult instrumental delivery with injury or death to the baby and the mother left with a vesical or rectal fistula or a permanently relaxed or damaged pelvic floor. Perhaps death. There is no fixed or predictable price.

In the day when mortality following section was 50 per cent, test of labor was mandatory and section barely thinkable. That day passed in 1882. Test of labor should have passed with it. It properly belongs with the thinking of 1882.

There is no omniscience in electing section. There is knowledge of the cost and knowledge of the outcome. Section electively performed carries a mortality of 0.5 per cent, and section thus performed will increase section incidence by 1.5 to 2.0 per cent.

In the matter of management of the patients exhibiting eclampsia, Dr. Waters states, "We do not perform cesarean

section on patients with eclampsia unless antitoxic measures have checked the eclampsia and made the patient operable." Now how is it known that the "antitoxic measures" have checked the eclampsia? How is it known that the patient has been made "operable"? What are the measures which have such virtue? If a convulsion is stopped medically has the eclampsia ceased? If measures stop convulsions, how predict the time at which the next will arrive? How long does Dr. Waters wait after eclampsia is checked before he operates? What criteria does he use to determine the operability of the patient?

Dr. Waters is to be congratulated on the excellent record of his clinic. His paper is of great value and certainly contains a wealth of provocative and stimulating matter.

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* * *

Dr. Schreiber's letter was referred to Dr. Waters, whose reply is as follows:

August 6, 1946

To the Editor: The wording of the referred-to paragraph is sufficiently explicit, I trust, even to the omniscient, to clarify our attitude with respect to test of labor. Dr. Schreiber determines *in advance of labor*, after considering "all available data including accurate clinical and x-ray mensuration and the excellent procedure of Hillis" whether or not a patient requires a cesarean section. Since none of us may possess the fundamental obstetric data which I referred to but which all of us, including Dr. Schreiber, must at least consider, it is clear that he qualifies most excellently as one of the "omniscient" and can find his companions in the literature with no help from me.

The picture Dr. Schreiber paints of the patient who has been given a test of labor is harrowing and pitiful, even though nonexistent, at least in our clinic. With adequate analgesia, supportive ante-partum therapy and careful labor observation, there is no reason why such patients should be exhausted, dehydrated, infected or poor surgical risks. If a gross error of judgment is made, which on occasion seems well within our experience, there are suitable operative procedures which minimize the risk and approximate the mortality given by Dr. Schreiber for purely elective section.

In my own private service I have had no maternal cesarean death in more than fifteen years following *any* type of cesarean operation. With rare exceptions, I invariably allow primiparas enough labor to demonstrate the effectiveness of the normal mechanism, and if the hours of labor and ruptured membranes exceed our safety period, I resort to extraperitoneal section — which even then is as safe as the elective operation. To me, a test of labor so conducted is a cheaper "commodity" than *increasing* the general cesarean incidence by 1.5 to 2.0 per cent, and I question the quoted 0.5 per cent mortality for elective cesarean section if applied to the country at large.

I trust those who read Dr. Schreiber's letter will also read my article and study the tabular data given on eclampsia, which should satisfy the questions asked. Most patients who have eclampsia will deliver vaginally. But an independent indication for section may be present, or the patient may fail to maintain improvement after a seeming happy response to initial therapy. Cessation of convulsions, recovery from coma and stupor, clearing of the pulmonary passages, lowering of blood pressure and pulse rate, and restored urinary output will serve notice that operation may be assayed under spinal anesthesia in the needed case, but with an accepted risk by virtue of the eclamptogenic toxemia itself. Experience with enough clinic and post-mortem material teaches that no didactic answers may be made to Dr. Schreiber's questions on eclampsia. We are guided to such answers by the considered results of experience over years as applied to *each eclamptic patient*, and the efficacy of our scientific guessing or balanced judgment as you will may be determined from the data I submitted. That, I believe, speaks sufficiently well for itself.

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Jersey City 4, New Jersey

BOOK REVIEW

A Manual of Surgical Anatomy. By Tom Jones and W. C. Shepard. Prepared under the auspices of the Committee on Surgery, Division of Medical Sciences, National Research Council. 4°, cloth, 195 pp., illustrated. Philadelphia and London: W. B. Saunders Company, 1945. $5.00.

This excellent manual measures up to the high purposes for which it was developed. In the words of Major General Norman T. Kirk, the surgeon general of the Army, the aim of the manual is "to provide a concise atlas of applied surgical anatomy which permits rapid visual review of any part of the body and the proper surgical approaches to the various regions to the surgeon who may be called upon to perform urgent surgical procedures on the wounded." The drawings, arranged regionally, are from the skillful hands of the expert artists Jones and Shepard. The illustrations are simple line drawings, with the names placed on the various structures themselves. Inasmuch as good surgery depends, to a large extent, on thorough familiarity with the anatomy and structural relation of the parts involved, a careful thoughtful study of the illustrations will serve the best interests of the surgeon. There is a useful fifty-four-page explanatory index. The text is divided into four parts: head and neck; trunk-thorax, abdomen and pelvis; upper extremity; and lower extremity. This book makes a definite contribution to medical and surgical thought and merits a wide reception.

NOTICES

DIABETES CLINIC

Eli Lilly and Company will sponsor a diabetic clinic to be held at the Indiana University Medical Center in Herty Hall of the State Board of Health Building, Indianapolis, Indiana, on September 23 — a week following a program at the University of Toronto in honor of the twenty-fifth anniversary of the discovery of insulin. International importance will be given to this meeting by the presence of Professor Charles H. Best, of Toronto, Canada, Professor Bernado A. Houssay, of Buenos Aires, Argentina, Dr. R. O. Lawrence, of London, England, and Dr. H. C. Hagedorn, of Gentofte, Denmark. Various phases of diabetic care will be discussed.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, SEPTEMBER 5

TUESDAY, SEPTEMBER 10

12:00 m.–1:00 p.m. Dermatological Service, Grand Rounds. Amphitheater, Dowling Building, Boston City Hospital.

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

WEDNESDAY, SEPTEMBER 11

*10:30–11:30 a.m. Medical Clinic. Isolation Building Amphitheater, Children's Hospital.

*12:00 m. Clinicopathological Conference. (Children's Hospital.) Amphitheater, Peter Bent Brigham Hospital.

*2:30–4:00 p.m. Combined Clinic by the Medical, Surgical and Orthopedic Services. Amphitheater, Children's Hospital.

*Open to the medical profession.

MARCH 15–SEPTEMBER 15. Boston University Course for Discharged Medical Officers. Page 240, issue of February 14.

SEPTEMBER 4–7. American Congress of Physical Medicine. Page 616, issue of May 2.

SEPTEMBER 5. New England Hospital for Women and Children. Page 284, issue of August 22.

SEPTEMBER 12. Bronchiectasis and Pulmonary Abscess: Diagnosis and treatment. Dr. Maurice Segal. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

SEPTEMBER 16–18. American Diabetes Association. Page 284, issue of August 22.

SEPTEMBER 23. Diabetes Clinic. Notice above.

SEPTEMBER 30–OCTOBER 2. Congress on Industrial Health. Page 284, issue of August 22.

OCTOBER 6–12. Interamerican Congress of Cardiology. Page xix, issue of June 6.

OCTOBER 7–12. Seminar in Legal Medicine. Page 206, issue of August 8.

(*Notices continued on page xiii*)

NOTICES (*Continued from page 314*)

October 7–18. New York Academy of Medicine. Page 544, issue of April 18.

February 7. American Board of Obstetrics and Gynecology. Page 238, issue of August 15.

April 28–May 2. American College of Physicians. Page 206, issue of August 8.

District Medical Society

PLYMOUTH

October. Jordan Hospital, Plymouth.
November. Plymouth County Hospital, South Hanson.
January. Brockton Hospital, Brockton.
February. Moore Hospital, Brockton.
March. Goddard Hospital, Brockton.
April. State Farm, Bridgewater.
May. Lakeville Sanatorium, Lakeville.

BOSTON CITY HOSPITAL

Postgraduate Courses

Refresher Course in Medicine. This is a sixteen-week course conducted by the Boston University, Harvard and Tufts medical services of Boston City Hospital. The course is designed to emphasize practical instruction. It will consist of a clinical clerkship on the medical wards (eight weeks) and special medical clinics in the Out-Patient Department (eight weeks), under supervision of instructors from all three teaching units. In addition, daily formal exercises including clinics, conferences and lectures will be held which all students will attend. Enrollment for this course will be limited to twenty-four students (eight to each teaching unit) for each sixteen-week period. No special books will be required for this course. **Fee $230.00.**

Refresher Course in Pathology. This course will comprise a twenty-four-week review of autopsy and surgical material at the Mallory Institute of Pathology under the supervision of Drs. F. Parker, Jr., G. K. Mallory and S. L. Robbins. The systematized review of pathologic anatomy will include lectures, conferences and participation in autopsies and the examination of surgical specimens. The course is designed to give a thorough postgraduate training in pathology, with a view to satisfying the needs of the various American specialty boards. It is limited to eight members for each twenty-four-week period. **Fee $350.00.**

These courses begin on October 1, 1946, and are open to all properly qualified physicians. They have been approved by the Committee for Hospital Training Programs under Public Law No. 346 (Further Training of Veterans).

Requests for application blanks or further information should be addressed to Dr. John P. Rattigan, Co-ordinator of Interns, Boston City Hospital, 818 Harrison Avenue, Boston 18.

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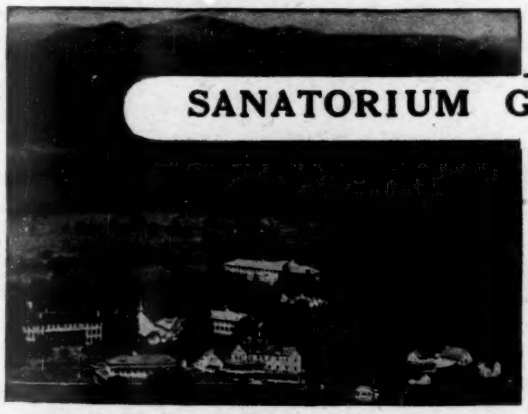

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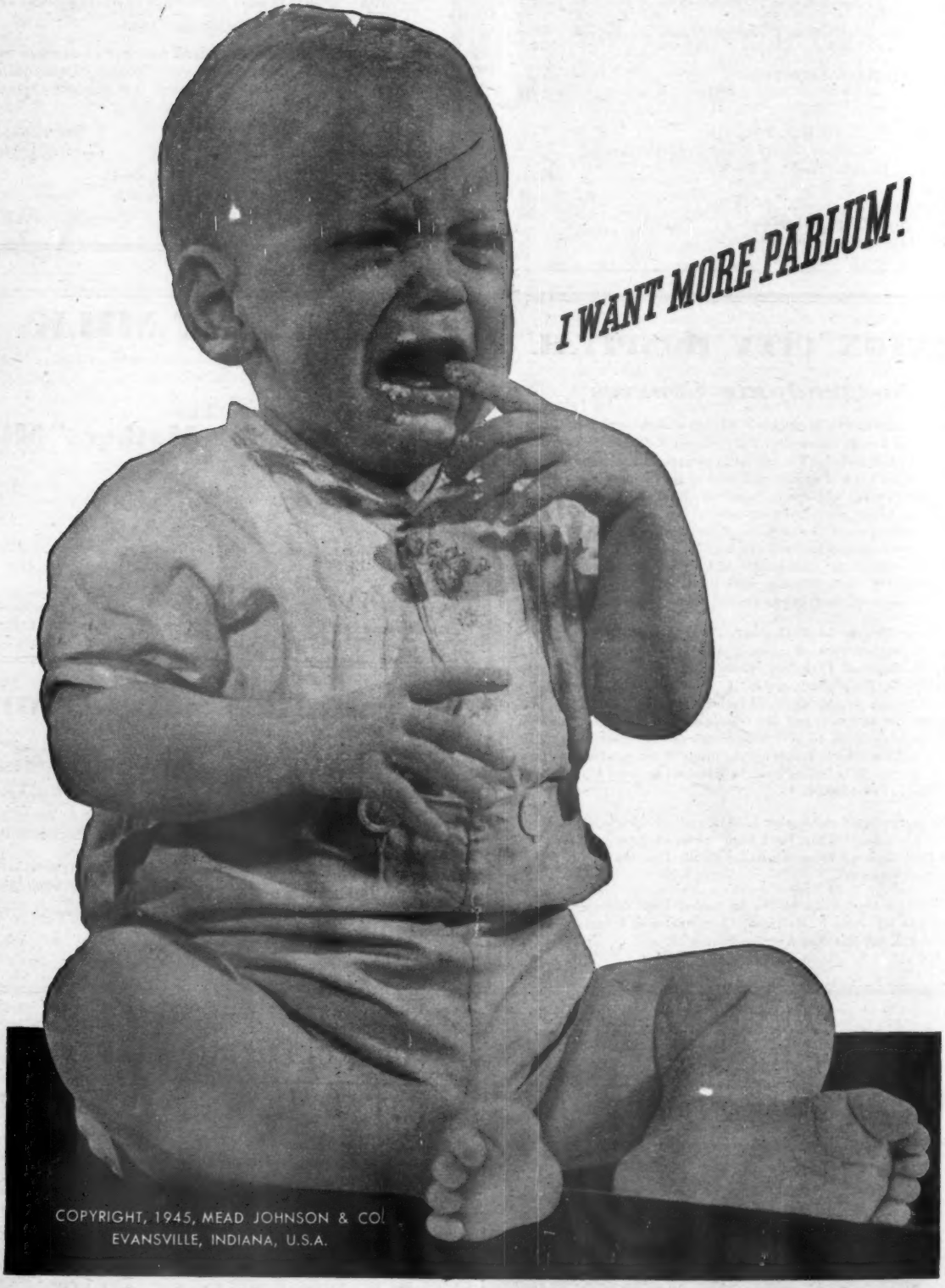
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